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THE INDUSTRIAL HEALTH MOVEMENT WITH SPECIAL REFERENCE TO DERMATOSES

CHAIRMAN'S ADDRESS

John Eric Dalton, M.D., Indianapolis

A recent opportunity to study the cutaneous reactions occurring among a group of pharmaceutical workers [1] led me to become interested in the general medical and economic problems created by the industrial dermatoses. Since writings on the ramifications of this subject are found to a great extent in the developmental history of employer-employee relationships and in the general industrial health surveys, in order to set the stage for a later discussion of work-associated skin ailments it may be well to review the facts known and attitudes held regarding the whole group of disabilities which affect wage earners.

HISTORY OF GROUPS CONCERNED IN INDUSTRIAL HYGIENE DEVELOPMENT

The present state of our knowledge of and attitudes toward industrial health has evolved over the past century and a half. Many individuals and agencies assisted in the upbuilding of the industrial hygiene program, but for discussion purposes we will assemble these separate efforts under the headings of the seven group-units which have made the major contributions to this movement. They are, namely, (1) medical groups, which include doctors, dentists, and nurses, who are working independently of governmental sponsorship, (2) other professional groups, (3) labor, (4) management, (5) insurance companies, (6) private organizations, and (7) governmental agencies which are concerned with both the medical and nonmedical phases of this question. The source of the historical data in the following discussion is a late government publication.[2]

Medical Groups.—Medicine was called on to provide the professional personnel for these industrial health programs, to understand manufacturing processes and safety control methods, to introduce means of preventing disability amongst workers, to treat injuries and disease in employees, to create a literature from their experience, to establish schools for the training of industrially minded medical or nonmedical individuals, to organize groups mutually interested in an interchange of opinions on this field, to set up ways of and standards for operating plant programs within both small and large industries, and to cooperate in various insurance plans paying benefits to sick wage earners.

The designation "Father of Industrial Medicine in the United States" can be applied to Benjamin W. McCready, M.D., who presented the first nationally recorded paper on occupational diseases before the Medical Society of the State of New York in 1837. This was titled "On the Influences of Trades, Professions and Occupations in the United States in the Production of Disease," but he drew heavily on the documented experiences of the English authorities in this field. Nothing of further significance appeared until 1860, when Addison Freeman, M.D., made a report on industrial mercurialism. In the decade following on 1879, an increasing number of articles on the general nature of these particular medical pictures were published. By 1914 sufficient knowledge and interest in this field had accumulated to lead to the appearance of the first text on occupational disease, by W. G. Thompson, M.D., and in that year and in 1916 and in 1919 three other books on the over-all problems of this special subject were announced. In 1925 Alice Hamilton, M.D., issued the first volume devoted to industrial toxicology, and in 1939, Louis Schwartz, M.D., produced the first text limited to occupational diseases of the skin. Among the authors of these special books, I would like also to mention Ralph Waldo Webster, M.D., who, in 1938, published a "Text on Legal Medicine and Toxicology." In 1919 enough papers dealing with industrial health were available to warrant the founding of the first periodical specializing in the publica-

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From the Department of Dermatology and Syphilology of Indianapolis General Hospital, the Alembert Winthrop Brayton Skin and Cancer Foundation and the P. C. Reilly Laboratory of Mycology.

1. Dalton, J. E., and Peirce, J. D.: Dermatological Problems Amongst Pharmaceutical Workers, A. M. A. Arch. Dermat. & Syph., to be published.
2. Klem, M. C.; McKiever, M. F., and Lear, W. J.: Industrial Health and Medical Problems, Public Health Service Publication no. 15, Federal Security Agency, United States Public Health Service, September, 1950.

tion of the current literature of this field. This was known early as the *Journal of Industrial Hygiene*, but in 1936 its name was changed to the *Journal of Industrial Hygiene and Toxicology*. A second magazine entered this field in 1932 under the title of *Industrial Medicine*, and here, likewise, we see it undergo a name change to *Industrial Medicine and Surgery* in 1949. Still a third publication, designated *Occupational Medicine*, appeared in 1946, but eventually all three of the existing magazines were combined in 1950 by the American Medical Association in a journal which is now known as the *A. M. A. Archives of Industrial Hygiene and Occupational Medicine*.

Special organizations for physicians engaged in the physicial well-being of workers date back to 1888, when the American Association of Railroad Surgeons was founded. In 1915 the American Association of Industrial Physicians and Surgeons was formed to elevate the standards of industrial medical practice. This movement was carried a step further, when, in 1926, the American College of Surgeons published an outline for Minimum Standards for Medical Service in Industry. Still later, the American Medical Association established, in 1937, a Council on Industrial Health to coordinate all the endeavors in that field, and this newly formed group arranged for the first Annual Congress on Industrial Health in 1939. At the present we find numerous medical groups with an active interest in the various phases of occupational and nonoccupational injuries and disease. Among these can be listed the Aero Medical Association of the United States, the American Academy of Compensation Medicine, the American Academy of Occupational Medicine, the American Academy of Dermatology and Syphilology, the American Academy of Ophthalmology and Otolaryngology, the American Association of Industrial Dentists, the American Association of Industrial Nurses, the American Association of Industrial Physicians and Surgeons, the American Association of Railway Surgeons, the American Association for the Surgery of Trauma, the American College of Surgeons, the American College of Chest Physicians, the American Heart Association, the American Medical Association, the National Tuberculosis Association, and the American Trudeau Society.

The first courses of instruction in industrial hygiene were given in 1905 by the department of biology and public health of the Massachusetts Institute of Technology. During the following year the Medical Department of the University of Pennsylvania gave emphasis to this same subject in the courses which led to their doctorate in public health. Further, they coordinated these lectures with the inspection of factories, a service in the first aid station of several plants, and an attendance in the cooperating clinics at the University Hospital. In 1910 the first occupational disease clinic in this country was instituted at Cornell Medical School, under W. G. Thompson, M.D., and in 1911 the University of Chicago and Rush Medical College jointly undertook a similar project under E. R. Hayhurst, M.D. Next to enter this branch of education was Harvard University in 1918, which outlined courses of instruction and research that resulted in the granting of a degree in industrial hygiene. The medical graduates attending these classes were also assigned to work in the occupational disease clinic at Massachusetts General Hospital. Since that time several other medical schools have introduced similar courses into their curriculum.

The first scientific symposium on industrial hygiene and medicine was held at the annual meeting of the American Medical Association in 1915. Also, the extensive studies on tuberculosis and other pulmonary diseases which were carried out in 1918 by L. U. Gardner, M.D., at the Saranac Laboratories of the Trudeau Foundation have been of great basic value to the understanding of these entities when occurring in industrial workers.

In 1933 the American Hospital Association approved the principle of group plans for the prepayment of hospital service, setting forth a list of essentials which should characterize such plans. The following year the American College of Surgeons endorsed insurance plans which covered both medical and hospital care. During 1939 we saw a new turn in the matter of health insurance. In that year both California and Michigan organized the first state-wide prepayment medical care plans that were sponsored by the state medical societies themselves. Since then other state associations of physicians have set up similar medical care projects connected with the hospital service plan of Blue Cross. All these appear to be succeeding, but time will tell if intelligent physicians can also be smart insurance men.

Nursing officially entered the field of industrial hygiene in 1895, when Ada Mayo Stewart was asked by the Vermont Marble Company to watch over the well-being of its workers. Shortly thereafter several mercantile stores made similar moves, and in 1909 the Milwaukee Visiting Nurse Association placed one of their number in a local factory for the purpose of demonstrating the value of a nursing service to an employer. The acceptance by management of these specially trained women grew steadily, and in 1913 the first registry for industrial nurses was opened in Boston to provide suitable nurses for first aid rooms in factories. A need for graduate education in this field arose, and therefore in 1917 the College of Business Administration of Boston University announced the first course designed specifically for industrial nurses. This and other factors stimulated Florence Swift Wright in 1919 to write a text which she titled "Industrial Nursing." The following year, the National Association of Public Health Nurses established an industrial nursing section, and in 1942 the American Association of Industrial Nurses was formed with the aim of improving the standards of nursing practices in industry. The Indiana State Health Department in 1939 was the first to use a nurse consultant in its industrial division. Thus, nursing, through the efforts of its fine women, has won well-deserved respect in industrial medicine.

Dentistry made its entry into this field in 1890. During that year the Barber Match Company invited one of this profession to set up a dental program for their employees, but for the next several years the use of this professional group was limited to isolated instances of this sort. However, in 1943 the American Association of Industrial Dentists was formed, and the dental profession will no doubt experience an increasing number of calls into the expanding medical care programs which are now sponsored both by factory owners and insurance companies.

Other Professions.—In the problems of industrial medicine, chemical, mechanical, and safety engineers have made many contributions to the reduction of hazards. Praise of their work has often gone unsung because many of their reforms in manufacturing procedures have been introduced in an emergency situation, and all these reforms have not been recorded. However, as we look about, there is no doubt that their experienced observation has done much for the refinement of machine design, the introduction of safety measures, and the understanding of noxious agents.

Further, many high-minded attorneys, judges, industrial referees, and legislators have been a force for good in this field. Through their efforts they have been instrumental either in writing the laws or enforcing the statutes which safeguard the interests and fix the responsibility both for labor and management in the legal controversies arising in industry.

Labor.—Labor's chief activity in the general problems of industrial hygiene has been to secure medical care and welfare measures for its ranks. To attain this end, benefit systems were set up by the Cigar Makers' Union in 1867, the Iron Molders' Union in 1870, the Granite Cutters' Union in 1877, and the Barbers' Union in 1895. Also, in 1868 a fraternal beneficiary society known as the Ancient Order of United Workmen was established which had for its primary purpose the assistance of members who were sick or totally disabled.

The first union-sponsored service type of medical care plan was started in 1913 by the International Ladies' Garment Workers' Union, and in 1917 the plan was incorporated as the Union Health Center. This group has probably been the most successful of them all and has only lately made further expansions to care for any worker and his dependents.

The first collective bargaining agreement providing life insurance and weekly sick benefits was negotiated in 1926 between the Public Service Corporation of Newburgh, N. Y., and the Amalgamated Association of Street and Electric Railway Employees. This contract contained both life insurance and sick benefits. In 1943 the first medical benefits other than weekly sick benefits included under a collective bargaining agreement became operative for members of the Philadelphia Waist and Dress Joint Board of the International Ladies' Garment Workers' Union. In 1947 the first medical services of the United Mine Workers' Welfare and Retirement Fund were provided, but this was only for those suffering from paraplegia.

Management.—The first major prepaid industrial medical care program was organized in 1868 as the hospital department of the Southern Pacific Railroad Company. It was financed jointly by employer and employees and now offers full service through their hospital in San Francisco and through agreement with physicians at other points along their line. A like movement was initiated by the Missouri Pacific Hospital Association in 1872 and by the Northern Pacific Beneficial Association in 1882. Then, in 1885, the Macy Mutual Aid Association was established, which in the following year secured a part-time physician to advise on sick benefit claims and to care for minor ailments in the members. This idea went a step further in 1887, when the Homestake Mining Company of Lead, S. D., formed a company-financed medical department with a full-time staff giving complete medical care to employees and their families.

One of the first instances in which a physician was appointed to do physical examinations in a group of workers took place in 1906 in a large saw works in Providence, R. I. The purpose of these examinations was to find any cases of tuberculosis among the employees. A like project was established in 1909 by Sears, Roebuck and Company of Chicago. Also, in line with this study of special ailments among workers, the Boston Elevated Railway in 1911 engaged a Harvard professor to conduct psychological tests on applicants for the position of street car motorman. A four-year study of the mental health problems of the employees of the R. H. Macy and Company of New York City in 1929 led to the report of a psychiatric team, titled "Psychiatry in Industry." In 1935 the anthracite coal operators of Pennsylvania joined with the United Mine Workers and the United States Public Health Service to do the first major study on anthracosilicosis among hard-coal miners.

Combinations of management now began mutual studies of various problems in their plants, and in 1921 the National Foundryman's Association issued a safety code for the protection of industrial workers in foundries. In that same year the Illuminating Engineering Society sponsored the publication of a safety code for the lighting of factories, mills, and work places. In 1936 some of the largest industrial concerns in the country joined with the United States Public Health Service, the United States Bureau of Mines, and the Mellon Institute to form the Air Hygiene Foundation, which was to be known later as the Industrial Hygiene Foundation, and in 1939 the American Industrial Hygiene Association was founded to provide a method for interchanging and developing the knowledge of industrial health. Also the National Association of Manufacturers has contributed considerably by some of its valuable studies.

Insurance Companies.—Strange as it may seem, private insurance made its debut into the health problems of workers with a program for dental care. In 1915 the Metropolitan Life Insurance Company established one of the oldest continuous programs in this field. In 1917 this same company cooperated with the Bureau of Labor in publishing their occupational mortality experiences for the 1911-1913 period. Then, in 1920, private insurance companies began writing group contracts for temporary disability benefits on nonoccupational accidents or sickness. Again the Metropolitan Life Insurance Company entered the picture in 1927, when they cooperated with other agencies to conduct a study on pulmonary diseases in workers at Picher, Okla. In 1929 the forerunner of Blue Cross Hospital plans was established in Dallas, Texas, when a contract for medical care was made between the teachers of that city and Baylor University Hospital. This was followed by private companies offering insurance against the costs of hospitalization in 1934, group surgical expense insurance in 1938, and group medical expense insurance in 1943. We have all seen the rapidity with which these plans have spread.

Private Organizations.—In 1906 the American Association of Labor Legislation was formed to conduct investigations, to hold conferences, to publish reports, to

establish standards, to draft bills, and to urge the passage of laws on working conditions, and in 1910 it arranged the first national conference on industrial diseases. The National Council for Industrial Safety, which was formed in 1913 to collect data on occupational and nonoccupational accidents and to foster accident prevention programs, established a Health Service Section in 1914, changing its name to the National Safety Council in 1915. Also, the American Public Health Association organized a Section on Industrial Hygiene in 1914.

Aside from numerous universities, there are active in the different phases of industrial hygiene the American Chemical Society, the American Industrial Hygiene Association, the American Public Health Association, the American Social Hygiene Association, the American Society of Heating and Ventilating, the American Standards Association, the Illuminating Engineering Society, the National Safety Council, the National Association of Manufacturers, the National Society for the Prevention of Blindness and the Industrial Hygiene Foundation.

Government.—Here, as in other governmental activities, we see health functions which began on a municipal level gradually taken over by state agencies and eventually passing to Federal bureaus.

The initial organized effort to combat illness in the population came in the formation of boards of health. The first of these agencies were set up locally, in Petersburg, Va. (1780), New York City (1796), and Boston (1799), but in 1798 the Federal Government entered this field by establishing the Marine Hospital Service for the care of American seamen, which was to be the forerunner of the United States Public Health Service. Although Louisiana, because of recurrent yellow fever epidemics, developed a short-lived state board of health in 1855, the first such organization to remain in continuous existence was formed by Massachusetts in 1869. Somewhat later the national administration recognized the general problems of management and workers by setting up the Bureau of Labor in 1844 and the Bureau of Mines in 1910. The health work of the latter bureau began in 1913 when it borrowed physicians from other agencies on a part time basis; eventually, in 1926, it appointed a full-time physician to carry on its medical activities. Concern regarding workers health had grown so by 1913 that both Ohio and New York established state industrial hygiene agencies which were staffed with both physicians and engineers. During the next year an Office of Industrial Hygiene and Sanitation was created within the United States Public Health Service, and in 1937 this became the Industrial Hygiene Division of the national Institute of Health of that service. In 1917 the above earlier-formed office joined with the Department of Labor to establish a Working Conditions Service, and this led to the setting-up in 1934 of a Division of Labor Standards in the Department of Labor, which reached full bureau status in 1948. During this time the Social Security Act of 1935 was passed, making Federal funds available to the United States Public Health Service for extending research and for making grants-in-aid to the states for public health work including industrial hygiene. As a result of this, several states began forming industrial hygiene units. With the expansion of these federal health agencies the American Conference of Governmental Industrial Hygienists was organized in 1938 to promote sound administration of governmental industrial hygiene activities, and in 1940 the National Defense Council appointed the Federal Security Administrator as coordinator of all medical and welfare questions affecting national defense. With the World War II emergency in 1942 all authority over employment and employment training was vested in the War Manpower Commission, which was headed by the Federal Security Administrator. In 1943 the present structure of the United States Public Health Service was defined and all laws pertaining to this service were consolidated.

Regulations regarding the employment of children and women and the hours of work to be spent by these and other employees have been one of the chief concerns of governmental groups. Many of these laws, instead of being all inclusive, apply to specific industries.

The first child labor act became effective in Massachusetts in 1836, stipulating merely that employed children under 15 years of age must have three months' schooling each year. Later (1842) this law was amended to forbid children under 12 years of age from working more than 10 hours a day in a factory, but the evasion of these regulations required the setting up of a police enforcement agency in 1867. Connecticut, likewise, in 1842 passed a 10 hour law for children under 14 working in cotton and woolen mills, and in 1849 Pennsylvania enacted a law forbidding the employment of children under 13 in a textile plant. In 1851 New Jersey banned the use of children under 10 years of age in any manufacturing plant, and this was followed by a lull in the adoption of such legislation. Then, in 1903, Illinois set an eight-hour work-day for children under 16, and within two years this was adopted by 22 other states. By an Act of Congress in 1906 the National Child Labor Committee was incorporated to check all data and to investigate conditions of and to promote legislation concerning the employment of children, and to educate the public on matters involving this employment. In 1909 the first White House Conference on Child Welfare was held, and in 1912 the United States Children's Bureau was set up to investigate and to report on all matters pertaining to the welfare of children. Eventually, in 1922, after two child labor acts were declared unconstitutional, the legislative bodies of the United States passed a Child Labor Amendment to the Constitution, but up to 1950 only 28 of the states had ratified this protective measure.

Women in industry have been the concern of legislators since 1847, when New Hampshire passed the first law regulating their work hours in manufacturing plants. In 1879 Massachusetts enacted the first enforceable law limiting a woman's engagement in an occupation to 10 hours a day and 60 hours in a week, and in 1890 it further prohibited service of such workers after 10 o'clock at night. Other states followed with regulations on the hours of work permitted for women, and in 1908 the United States Supreme Court upheld the constitutionality of Oregon's law limiting women to a 10-hour work-day as a health measure. The court reaffirmed this position in 1915, when it upheld the California law limiting women workers to an eight-hour day. Attention turned to the matter of employing women during pregnancy, and in 1911 Massachusetts was the first state to

forbid the employment of women within the two weeks before or the four weeks after delivery; other states have since followed with similar laws. In 1920 a Women's Bureau was created in the Department of Labor to watch over the general welfare of female employees.

Other provisions have been made by governmental groups for all workers. The 1847 law of New Hampshire concerning employed women had a clause limiting the work-day for all workers to 10 hours unless an express contract permitted a greater time. In 1868, the United States Government enacted a law providing for an eight-hour work-day for laborers, workmen, and mechanics who were employed by or on behalf of the government, and in 1912 another law made it necessary to insert an eight-hour work provision in all contracts which involved the employment of laborers or mechanics and which were made by, for, or in behalf of the Government of the United States or that of the Territories or the District of Columbia. Another Federal law, known as the Hours of Service Act, became effective in 1907, limiting the service of train employees and telegraph and signal operators on railroads, and in 1938 the Federal Fair Labor Standards Act set forth the maximum hours that could be worked by and the minimum wages that could be paid to workers in all industries engaged in interstate commerce.

The first safety regulations, which applied to steam engines, were passed by Massachusetts in 1852. The same state in 1877 enacted other measures dealing with factory safeguards, and in 1905 it made a study of the conditions bearing upon the health and safety of workers of that state. In 1907 the state of Massachusetts held the first industrial hygiene exhibit in this country, and in 1911 the American Museum of Safety, which later became the Safety Institute of America, was established in New York City with a department of industrial hygiene. In 1921 the United States Bureau of Standards issued a safety code for the protection of the head and eyes, and in 1938 it added a safety code for the protection of the respiratory organs. In 1933 a Federal statute known as the National Industrial Recovery Act was passed which contained clauses on hours and on safe and healthful working conditions, but it was declared unconstitutional two years later. In 1935 the issuance of a safety code for industrial sanitation in manufacturing establishments was sponsored by the United States Public Health Service. The Public Contracts Act of 1936 included provisions for the safety and health of workers.

After the establishment of the Marine Hospital Service in 1798, no further steps were taken in the field of Federal medical care by the national government until 1921, when, through the Sheppard-Towner Act, it provided grants to states to promote maternal and infant welfare and hygiene. In 1937 the Railroad Retirement Act included maternity and sick benefits among its provision. During World War II Federal grants were given in 1943 to state health departments for emergency maternity and infant care of wives and babies of specified grades of enlisted men of the Armed Forces, and the Federal Employees Health Service Act in 1946 authorized Federal departments and agencies to provide their employees with health service programs. Lastly, the Social Security Act Amendments of 1950 included provisions for the extension of coverage and an increase in benefits under old age and survivors insurance, an increase in the contribution rate for both employer and employee, and Federal grants-in-aid for assistance to needy persons who are permanently and totally disabled.

In 1886 Massachusetts put a statute on its books requiring the reporting of industrial accidents. California in 1911 enacted a law making the reporting of occupational disease compulsory. Since then an additional 25 states have written such laws. In 1902 Connecticut passed the first law barring workers with contagious diseases from employment. Massachusetts in 1911 forbade the use of any type of shuttle in the textile industry which required placing any part of the shuttle or the thread in the mouth or touching it to the lips of the operator; this legislation was aimed at protecting textile workers from tuberculosis.

In respect to the insurance phases of industrial illness, the first plan was established by New York City in 1857 in the form of disability and death benefits for its policemen. Alabama enacted an Employers Liability Law in 1885, and Massachusetts followed this example two years later. Then, in 1902, Maryland passed the first state law providing for state benefits to workmen injured at work without suit or proof of negligence, but it was declared unconstitutional. The first Federal law in this field was enacted in 1906 to compensate railroad workers in interstate commerce for injuries sustained in the course of employment. This was declared unconstitutional, but a revised bill passed in 1912. Another law granting the right of compensation to specified employees of the United States Government for employment-connected injuries was passed in 1908, and this was replaced in 1916 by one covering all Federal civilian employees. In 1909 Montana passed a law providing for a state cooperative insurance fund for workers employed in and around coal mines, but it was soon declared unconstitutional. Shortly thereafter the New York Employers Liability Commission reported its findings to the legislators of that state, and as a result a law providing both voluntary and compulory types of workmen's compensation was enacted. Although this statute was declared unconstitutional by the New York Court of Appeals, a compulsory law did become effective in 1914 after an amendment to the state constitution. In 1911 state workmen compensation laws were passed in Washington, New Jersey, California, Nevada, Ohio, Illinois, Wisconsin, Kansas, Massachusetts, and New Hampshire. By the Act of the State of Washington in 1911, a state insurance fund was created which was liable for compensation payments and which was maintained by compulsory contributions from employers, and, following this, other states established an elective type of workmen's compensation which had penalties for nonelection. In 1912 a Massachusetts court ruled that the wording of that state's Workmen's Compensation Act was sufficiently broad to include diseases springing from occupations. In 1917 the United States Supreme Court held that both compulsory and elective types of workmen compensation statutes are valid. In that same year Hawaii enacted a law making occupational disease compensable, and within the next two years three states passed similar legislation. In 1920 the Civil Service Retirement and Disability Fund was estab-

lished for Federal employees. In 1948 Workmen Compensation Laws became nation-wide by the enactment of such a law in Mississippi. The National Conference on Labor Legislation in 1950 advised an over-all Federal temporary disability law, but said that if federalization was not feasible, then the states should adopt disability insurance laws to provide for state funds to be maintained wholly by employer contributions.

This viewpoint of government on workmen's insurance has broadened. In 1942 Rhode Island enacted the first law providing cash benefits to workers for nonoccupational illness and injuries under their unemployment insurance law, and four other states have followed (California in 1946, New Jersey in 1948, Washington in 1949, and New York in 1949). Then in 1948 the National Labor Relations Board ruled that pension, health and welfare plans are within the scope of collective bargaining. This ruling was sustained by a court opinion in 1949. The Presidential Board of Inquiry in that same year concluded that social insurance and pensions should be considered a part of normal business costs to take care of temporary and permanent depreciation in, as they called it, the human machine.

Governmental surveys in industrial hygiene have been most worthwhile because within its various specialized agencies the government has the variety of personnel needed for the proper study of these problems. Most of these investigations have dealt with the hazards of specific agents, but others have been of a general nature.

As early as 1776 Benjamin Franklin had contended that a type of intestinal cramps developed in some persons as a result of drinking rum which had been produced by stills in which the head and worms were made of lead. In 1908 the Commission on Occupational Disease of the State of Illinois conducted physician-directed studies on lead poisoning, copper reactions, and caisson sickness, and in 1913 Ohio and Pennsylvania did similar investigations of lead. Since that time the United States Public Health Service has conducted surveys on workers exposed to radium watch dial manufacture (1924), tetraethyl lead gasoline (1925), benzol (1926), anthracosilicosis of mining (1935), air pollution (1936 and 1949), and hatters' fur (1941).

The first official industrial hygiene survey in this country was made in 1902 by C. F. L. Doering, M.D., for the Department of Labor, and the initial state-wide study of this problem was made in 1913 by E. R. Hayhurst, M.D., for the Ohio state board of health. The United States Public Health Service in 1914 studied pulmonary diseases among miners and the health status of New York garment workers, and the Bureau of Mines in 1941 inspected the health and safety of coal miners. In 1926 the United States Public Health Service with the cooperation of state and municipal agencies made a city-wide investigation of workers' health in Nashville, Tenn., and in 1940 they went on to make a similar comprehensive report on the nation. Regarding other phases of these general surveys, the United States Commission of Industrial Relations in 1915 issued a publication on its investigation of industrial unrest and labor-management relationship, and in 1917 the Bureau of Labor reported on the causes of death in workers. In 1919 the United States Public Health Service studied existing medical and surgical services in industrial establishments, and in 1921 the Bureau of Labor issued a text on "Occupational Hazards and Diagnostic Signs" by Louis I. Dublin and Phillip Loiboff, which they have since revised several times.

Aside from these surveys, several conferences have been held on various aspects of industrial hygiene. In 1912 the government sponsored the International Conference on Hygiene and Demography in Washington, D. C., which included a section on industrial hygiene. After a lapse of time, in 1934 the Department of Labor held the first National Conference on Labor Legislation, and in 1936 the same organization conducted a National Silicosis Conference. The United States Public Health Service, with other national governmental agencies in 1936, called a meeting of the Air Hygiene group and this was followed, in 1950, by the first technical conference on Air Pollution. Through Federal instigation the first National Conference on Industrial Safety was held in 1948, and the White House sponsored a Conference on Aging and Youth in 1950.

Attention was first paid to worker rehabilitation by a Federal Act on Vocational Rehabilitation in 1918. Following this New Jersey established six rehabilitation clinics for industrial workers in 1919. In 1950 the National Conference on Workmen's Compensation and Rehabilitation met in Washington, D. C.

GENERAL INDUSTRIAL DISABILITIES

During the past decade, the United States experienced a phenomenal rise in its total employment and the value of its produced goods. In 1949, which is the last full year for which complete figures are available, the labor force in this country numbered 58,710,000 persons.[3] and this group received aggregate earnings in wages, salaries, and supplements of $140,555,000,000, or an average of $2,869 per full-time employee.[4] In that same period the market value of produced goods and services attained a gross of $256,000,000,000.[5] However, to maintain these high production and earning levels, it is logical that we must keep an optimal degree of physical, mental, and environmental fitness among workers and their families.[6]

Surveys vary in their methods for obtaining data on the incidence of general disabilities among the labor force, and they are not uniform in their procedures for recording their findings. Thus, some of the quoted estimates may seem amazingly high, but they do indicate the increasing magnitude and complexity of industrial health problems.

Among the reports recorded on the basis of days absent from occupation, Heiser [7] stated that in 1940 ailments of some type caused an average loss of 9½ days per worker per year, or a total of 160 million man-days per annum, and a similar survey published in 1948 esti-

3. Annual Report on the Labor Force 1949, United States Department of Commerce, The Bureau of Census, March 2, 1950, p. 16.

4. Basic Data on the National Economy: Survey of Current Business, Department of Commerce, Bulletin 30, July, 1950, pp. 9, 15 and 16.

5. The Economy in Adjustments: A Review of 1949 Survey of Current Business, Department of Commerce, Bulletin 30, February, 1950, pp. 1 and 3.

6. Charron, K. C.: Changing Concepts in Occupational Health, Industrial Health Review 2:20 (Oct.) 1950.

7. Heiser, V. G.: Industrial Health Practices: A Survey of 2,064 Industrial Establishments, New York, National Association of Manufacturers, 1941.

mated this same figure at nine days.[8] In 1947 the Standard Oil Company of New Jersey and its affiliates reported that absenteeism due to sickness amounted within their own units to an annual average per employee of 3.63 days in their South American complements and 6.91 days in their North American branches over a 10-year period.[9]

Using a slightly different method of study, a Public Health report alleged that in 1940 there were 502,000 workers away from their job daily owing to various disabilities, and that this totaled 26,092,000 weeks, or 1.2% of the full work-time of the 45 million persons regularly employed during that year.[10] In 1947 the Research Council for Economic Security figured that 754,000 gainfully employed persons were off duty daily because of some illness, and that this amounted to 39 million work-weeks yearly.[10] Then, in February, 1949, the Census Bureau Current Population Survey added questions regarding disabilities to their forms, and this revealed that there were approximately 4,569,000 fourteen to 64-year-old, noninstitutionalized persons who were unable to work owing to an ailment or disabling condition on an average day of that particular month.[11] By a further study of that questionnaire, it was established that 55% had been off duty for three months or longer, 44% had been off duty for less than three months, and in the remaining 1% no duration was set. In 1949 Sappington quoted from an unpublished 1943 study which stated that a million workers are disabled daily.[12]

Likewise, we see a variety of figures given as the cost of industrial disability. However, wage loss, medical care, workmen's compensation, additional benefits, reduced production, material spoilage, employee replacement, and other associated expenses enter as separate items in such surveys. The final recorded amounts will vary according to whether one, several, or all of these factors were included in that particular study.

In regard to the wage loss alone from absences due to sickness, Sappington [12] called attention to a 1943 paper which set this figure at $7,690,000 for that year, and about the same time the Illinois Department of Labor reported that the workers of their state lost yearly about 3.2% of their income because of various disabilities.[10] A similar study of that period placed the cost of illness to workers themselves at 3 to 4 billion dollars annually,[10] and Strow [13] in 1947 set the average annual wage loss due to illness at 1½ to 4 billion dollars.

A late figure, limiting itself to the cost of the disabling illness in workers, was given as 2½ to 3½ billion dollars by the Research Council for Economic Security.[10]

When we consider the full outlay made by labor, management, and others because of absenteeism due to sickness in workers, we reach rather staggering amounts. In 1943 this was estimated to be approximately 15 billion dollars per year, and in 1947 a similar study figured it to be 10 billion dollars annually, or a per capita cost of $70 for every member of our population.[10] During the next year the Federal Security Agency in a report to the President alleged that sickness and disabilities cost 27 billion dollars in national wealth.[14] The Industrial Hygiene Foundation of America lately estimated that an annual expenditure of 75 million dollars is made in this field by industry, of 5 million dollars by the Federal Government, and of a certain amount of their tax receipts by the separate states.[12]

All the above estimates on lost time and disability costs may be influenced by several factors. The incidence of accidents, injuries, and illness in workers will vary from one type of industry to another, and between companies engaged in the same type of work but located in different areas.[7] Further, increases in absenteeism are traceable to seasonal inclemency, inexperienced help, certain personalities, low income groups, racial instabilities, women workers, and aged employees.[13] These create additional problems for the employer. Weather is uncontrollable, and the reduced number of job seekers in a period of almost full employment has made it necessary for management to accept these greater-risk groups in the hope of satisfying the constant demands for expanded production. The present labor shortage has even set into motion plans to rehabilitate former workers who have sustained some total occupational or nonoccupational ailment [1] and to find selected duties for those persons who were previously rejected because of a known defect.[8] The expense of general disabilities will vary with the hazards of the industry, the rates of illness, the operational cost of medical care programs, the payment of compensation and other benefits, the level of wage scales, the prices of living, and the reduced production.

The cost of any type of partial or total disability affecting a worker is borne jointly by the employer, the employee, and the public.[15]

For the company any employee absenteeism results in lowered production, and it is alleged that such incidents produce a monetary loss to the employer which is one and one-half times greater than the wage loss of the employee.[10] An additional matter, which is often forgotten, is that if the nature of this ailment precludes a return to this particular job the employer and all industry has lost a trained person. Further, it must be remembered that the injudicious recommendation of a department transfer for the worker is both costly and sometimes difficult for the employer. A certain company, which I serve, estimates that it costs $250 to conduct their preplacement examination of a candidate and carry him through a 90-day training period. Thus, if something happens shortly thereafter which necessitates separation of the newly trained person from his job, then the company has lost the money invested in that individual and must spend a like sum to place another worker in this assignment. Of course, the loss is inestimable if the person is an efficient employee of long service.[16]

8. Small Plant Health Service, Industrial Health Bulletin, vol. 4, no. 3 (Dec.) 1948.

9. Standard Oil Company of New Jersey and Affiliates: A Biometric Study of 10 Years' Medical Service, Standard Oil M. Bull. **7**: 57, 1947.

10. Disability, Publication 31, Research Council for Economic Security, Chicago, 1947.

11. Woolsey, T. D.: Estimates of Disabling Illness Prevalence in the United States, Pub. Health Rep. **65**: 163, (Feb. 10) 1950.

12. Sappington, C. O.: Health at Work, Indust. Med. **18**: 117 (March) 1949.

13. Strow, C. W.: The Extent and Economic Cost of Disability, Publication 23, The Research Council for Economic Security, Chicago, 1947.

14. Ewing, O. R.: The Nation's Health: A Report to the President, Federal Security Agency, United States Public Health Service, 1948, pp. 26-27.

15. Strow,[12] Black, S. B.: Industry Needs Medicine and Vice Versa, Occup. Med. **5**: 285 (March) 1948.

16. Peirce, J. D. Personal communication to the author.

For the employee, disability creates a problem which will vary in degree according to the occupational or nonoccupational character of his ailment, his age, and the length of his service. If he is new in this field and if his trouble is ruled as work-associated, then his illness will be covered by compensation, and a transfer to another plant department or a severance from that employment will not cause the loss of the higher wage scales gained after long experience. However, if the worker has served long with this industry, if he has developed a high degree of proficiency and if his illness springs from his job, then, though he is compensated for this episode, he still faces the penalty of a lowered income, because of the necessity of a plant transfer to another job in which he has no training or severance from the position in which he has become proficient and acquired seniority. The person who punches the clock and who falls victim to a nonoccupational disability pays twice—once for the medical bills and again in lost wages.[17] Work absence not covered by any type of benefits reduces the living standard of the absent wage earner and his dependents.

As stated above, the public shares also in this bill. Naturally, management-incurred expenses, such as lowered production resulting from absenteeism, the operation of full or partial welfare programs, and the payment of compensation or other benefits, are passed along to the consumer in the price of the finished product. Also our general economy is affected by the reduced buying power of that worker and his family.

INDUSTRIAL DISEASES

When we attempt to find reliable statistics of a nationwide character on occupational diseases alone, it is difficult. Although 26 states require the reporting of such episodes, the rulings are not followed. Information collected on such incidents from 18 states for the year between July, 1947, and June, 1948, showed only 31,400 such cases recorded. Furthermore, only 5% of these came as reports to state departments of health and the remaining 95% represented either claims entered for compensation or morbidity reports made to compensation agencies, which were in turn referred to the industrial hygiene divisions of these states. From this scanty data, it was determined that occupational disease accounted for only 2% of the total disabilities springing from industrial causes.[18] At any rate, work-associated illness probably plays but a minor role in the total absenteeism due to medical causes.[10]

NONOCCUPATIONAL DISABILITIES

It is quite evident, from the various surveys, that the greatest number of disabilities among workers occur as a result of nonindustrial injuries or illness,[2] and one study states that 90% of these episodes are not work-associated.[8] It was quite uniformly found that respiratory and digestive disturbances led this list.[9] Where one day of absence was caused by an occupational disease, 59 days were lost due an industrial injury and 855 days were missed because of a non-work-associated disability.[7]

MEDICAL PROGRAMS AND EXAMINERS' PROBLEMS

For specific outlines of suggested industrial health program plans, one is referred to the publication of the American College of Surgeons.[19] The value of these programs is shown in the data of that booklet and in the extensive studies made for the National Association of Manufacturers.[7] Certainly a system of preemployment examinations and physical rating aid in the proper placement of the employee, and periodic checkups foster his continued efficiency. Further, Heiser's report revealed a reduction of 62.8% in industrial disease cases, 44.9% in work accidents, 29.7% in plant absenteeism, 28.8% in compensation premiums, and 27.3% in labor turnover. By these lowered morbidities and the reduced mortalities, the worker's life span has been raised to 62.4 years, which is the average for the general population. For these programs to be fully effective they must contain both curative and preventive measures.

The cost of industrial health programs will vary according to the number of persons employed by the specific company and the status of the economy during the period in which the study is made. It is known that with the expanding features of these plans the total expenditures are increasing.[20] Although the per capita expense in a large factory when compared to that in a smaller plant is smaller, the over-all outlay is greater. An estimate made from the figures of 2,064 industrial establishments in 1940 set the annual cost roughly at $12 for each employee, but other surveys have set the figure higher. In a 500-man plant, when all the economical features of a well-directed company health program are considered, management can net a yearly saving of $5,611 above the operational expense of such a plan.

With the decrease in occupational accidents, the fields of work-associated disease, and particularly nonindustrial illness or injury, are assuming a primary position. For this reason it may be well to examine the existing policies in most plant health programs and to ask if these departments could render a more efficient service by placing an internist in direction and allow him the privilege of using other medical specialists in consultation. In a company of which I have a personal knowledge this plan has worked well and at a reasonable cost.[16]

The physician who is asked to rule on the occupational or nonoccupational nature of a presenting disability accepts considerable responsibility. He should have an intimate knowledge of industrial entities, the general working conditions of the particular plant, and the special manufacturing processes involved. By this, the doctor can determine if the patient can be treated while still at work, if he must be removed temporarily for proper care, if he will have to be severed from his employment, and how soon he can be returned to his job. All of these questions are of economic importance to both the worker and the company. It is stated that lost time is three to five times greater if a worker is treated by a physician who is unschooled in the seeing of industrial cases.[21]

17. Chiver, J. H.: The Need of Medical Service in Small Industry, Illinois M. J. **99**: 68 (Feb.) 1951.

18. Bloomfield, J. J.: Industrial Hygiene: A Series of Lectures on the Principles and Practices, Federal Security Agency, United States Public Health Service, Division of Industrial Hygiene, 1950, pp. 11 and 12.

19. Hess, G. R.: Medical Service in Industry and Workmen's Compensation Laws, ed. 2, Chicago, American College of Surgeons, 1946.

20. Thorpe, J. J.: Plantation Pipe Line Program, Standard Oil M. Bull. **3**: 339, 1950.

21. O'Connor, R. B.: Establishing a Modern Plant Medical Program, Indust. Med. **15**: 608 (Oct.) 1946.

Further, the medical examiner must insist on being given the time and privilege to use all the clinical and laboratory measures necessary for arriving at a proper diagnosis, and he must keep accurate records because of the possibility of subsequent litigation. Unfortunately, there are still a few industrial concerns and insurance carriers who do not want anything declared of industrial origin, and, on the other hand, there are some workers and a limited number of attorneys who want everything ruled occupational. These influences must remain unheeded because the final medical opinion may have to be defended in court even if the unbiased medical testimony is to the disadvantage of either or both of the contending parties. Because of such suits, we are seeing a more frequent use of physicians who are specially trained in the medical field which is involved in the particular industrial question of that case.

INDUSTRIAL DERMATOSES

Again we are confronted with both preventive and curative problems. A complete industrial health program includes protective measures consisting of a well-organized and full-time staffed dispensary, an alert personnel in safety direction, cooperating and intelligent departmental heads and supervisors, careful screening of work applicants, job and general plant training programs, cleanliness and orderliness in the factory, plant supplied and laundered work clothing, protective attire for certain specific assignments, adequate hygienic and recreational facilities for employees, proper suction and ventilation systems in production areas, temperature controls in work sites, enclosed methods of manufacture where needed, alarm and checking apparatus in hazardous locations, and other health and safety advances. However, it is well for management to be vigiiant in watching that employees use the facilities supplied.

Industrial skin ailments may arise from either primary irritants or sensitizers, and sometimes repeated cutaneous insults by a primary irritant may lead to sensitization.[6] A common basis for these manifestations lays in the use of oils, greases, solvents, acids, alkalis, paints, cleansing agents, and various chemicals used in manufacturing processes, some of which act solely by defatting the skin. If one suspects a primary irritant as a causative agent, it may be necessary to furlough the affected individual from work or to transfer him to another department until his ailment has cleared or improved, and then watch him closely for any recurrence or aggravation on return to his former duty. If a sensitizer or a sensitizing primary irritant is in question, then, after the acute phase of the ailment has subsided, one must go through careful and complete patch testings with the job contactants of the affected person in the concentrations specified in published lists on this subject,[22] but sometimes the picture will be further complicated by poly- or cross-sensitivities to other substances handled at work or in his outside environment.

According to a survey by the Standard Oil Company of New Jersey [9] and other studies, the most commonly occurring industrial dermatoses, aside from various types of venenation, are furuncles, cellulitis, abscesses, and dermatophytosis. However, one should probably ask if the diagnosis of the last entity was established by direct examination or culture of cutaneous material.

The incidence of work-associated dermatosis among the whole field of skin diseases has been variously estimated at from 2 to 20% by different observers.[22a] Here again one finds a variance in prevalence from one type of industry to another [22a] and in companies engaged in the same kind of work but varying in geographic situation.[23] However, industrial dermatoses are said to be just as frequent among individuals engaged in domestic or personal service or food handling as it is among factory workers.[22a] According to the study of a large oil company, cutaneous disturbances stood in fifth place amongst the diseases affecting their workers,[9] and in all industry, work-associated dermatoses are said to account for from 60 to 65% of all occupational illness.[24] It is said to occur annually in 1% of all industrial workers,[22a] and, in the survey by the above oil company, it showed a 50% increase during the 10-year period of study of their employees.[9]

Figures on lost time caused by industrial dermatosis were established by the Standard Oil Company of New Jersey as accounting for 0.23 days per employee in their North American branches and 0.28 days per employee in their South American complements.[9] Schwartz and his colleagues estimate the average lost time for each case of occupational skin disease is 10 weeks.[22a]

The cost of these entities in lost time, medical care, and compensation runs into the millions.[6] By a study of compensation records, it was estimated that industrial cutaneous disabilities in the United States cost 100 million dollars annually ($100 per case) and that the medical care expense for these patients averages $90 per person.[22a]

Between Nov. 1, 1948, and Nov. 1, 1950, ninety-eight cases were referred by a large pharmaceutical manufacturer for a dermatological opinion.[1] Seventy-four of those patients were ruled as having some nonoccupational cutaneous disorder, and 24 were proved to have a plant-associated skin manifestation. The cost of these consultations and the subsequent visits of the industrial cases totaled $2,300. The average for the nonoccupational cases was $20, and for the occupational group it was $34.37. Only three of the 98 patients lost time because of their skin complaint. In that group, they lost a total of 56 days, they were paid wages of $483.21 during their absenteeism, and the medical costs amounted to $113.75. Furthermore, not a single employee filed a suit before the Indiana Compensation Board during this period.

SUMMARY

1. The history of industrial hygiene is recorded under the groups having to do with its development.

2. The ramifications of all work-associated disabilities are considered.

3. The difficulties arising from occupational diseases as a whole are discussed.

4. The general problems of industrial dermatoses are presented.

23 E. Ohio St.

22. (*a*) Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, ed. 2, Philadelphia, Lea & Febiger, 1947, pp. 27-30. (*b*) Sulzberger, M. B., and Baer, R. L.: Skin Tests and Other Immunologic Procedures in Common Dermatologic and Venereal Diseases, Chicago, The Yearbook Publishers, 1945, part I, pp. 7-47, 1943; part II, pp. 7-28, 1944; part III, pp. 7-36.

23. Brinton, H. P., and Schwartz, L.: Dermatitis Cases Reported Among Workers in Seven States, Indust. Med. **14**: 617 (July) 1945.

24. Charron.[6] Schwartz et al.

PROSTATECTOMY IN THE AGED

CHAIRMAN'S ADDRESS

John A. Taylor, M.D., New York

During the first decade of my practice—1924 to 1934—age per se was a definite contraindication to open prostatectomy. Young,[1] of Johns Hopkins Hospital, had an over-all mortality of 3.4%, while for patients over 80 it was 16%. Cabot [2] wrote: "Great age is a serious complication. The mortality from 50 to 60 and 60 to 70 is about the same. After 75 it increases very rapidly. Between 80 and 90, it is three times as great as 60 to 70." Swan and Mintz,[3] reporting cases from the Massachusetts General Hospital for the four-year period 1926-1930, showed that on only one patient over 80 had the operation been done in that period. During this decade the resectoscope was revived and revised. It proved a great boon for the aged who suffered with prostatic obstruction. Latchem and Emmett [4] in 1945 reported 345 cases of patients 80 or over with nine deaths, or a mortality of 2.6%. One recognizes at once that, with the improvements in anesthesia, with blood banks, with better understanding of biochemistry and fluid balance, and with antibiotics, open prostatectomy today is not so fraught with hazard and the mortality and morbidity associated with it have been greatly reduced. It is unfortunate that in a recent splendid review [5] based on questionnaires sent to members of the American Urological Association concerning all methods of surgical approach to the prostate the cases were not broken down into age groups. It is to be hoped that such an analysis will be forthcoming. In my hands, however, transurethral resection in the aged carries much less mortality and morbidity than does open operation and is considered to be a surgical procedure with minimal risk.

In 1948 I [6] reported on a series of 1,066 consecutive transurethral resections which had been done by the various members of the attending staff at St. Luke's Hospital between 1935 and 1945, the years representing the second decade of my practice. While there were five deaths in this series, for an over-all mortality of 0.4%, it was surprising to find that these deaths occurred in the younger age group—to wit, between the ages of 58 and 67 years—in spite of the fact that there were 376 patients over 70 years, 181 patients over 75 years, and 61 patients over 80, the oldest being 96 years of age. There were 90 operations performed in these 61 cases. It was a perusal of these facts, together with the recent experience of operating successfully on a 92-year-old man, that led to the subject for this address.

Since 1945 at St. Luke's Hospital, 41 operations in 35 cases of patients over 80 years of age have been performed on the ward service by the attending and resident staffs, and 27 operations have been performed on 24 of my private patients over 80. These cases added to the former reported series make a total of 158 operations on 120 patients over 80 and form the clinical material for this address.

AGE AND INCIDENCE

It can be stated here that these cases represent all the patients over 80 years of age who came to us for help. It has been noted in several reports on surgery of the aged that sometimes as many as 20% of the patients were considered unfit for surgery and were condemned to a catheter life. In our hospital we have figuratively ground all grist that came to our mill. No patient was considered too bad a risk for stabilization and subsequent surgery. The age distribution was as follows: 80 years, 23 cases; 81 years, 21 cases; 82 years, 17 cases; 83 years, 18 cases; 84 years, 4 cases; 85 years, 7 cases; 86 years, 10 cases; 87 years, 3 cases; 88 years, 8 cases; 89 years, 3 cases; 90 years, 2 cases; 91 years, 2 cases; 92 years, 2 cases; 96 years, 1 case.

PATHOLOGY AND ASSOCIATED LESIONS

In this series there were only 10 cases of carcinoma of the prostate, representing 8% of the total. This is a low incidence for malignancy and suggests that the carcinoma cases have a fatal termination before the patients enter the 80's. The last 65 cases in which operation was done since the previous report showed the following associated pathologic conditions: vesical calculi, 4 cases; papilloma, 4 cases; nephrocalcinosis, renal calculi, and chronic azotemia, 2 cases; arteriosclerotic heart disease with fibrillation, 2 cases; bundle branch block, 4 cases; coronary occlusion, 3 cases; pericarditis, thromboangiitis obliterans, thrombophlebitis, cerebral arteriosclerosis, healed pulmonary tuberculosis, silicosis and preoperative bronchopneumonia, 3 cases; Paget's disease, 2 cases; hernia, 6 cases; hemorrhoids, 2 cases; Parkinson's disease, 2 cases; glaucoma, carcinoma of the pancreas, stricture of the esophagus, and basal cell carcinoma, 1 case each.

The most constant associated pathologic state was a generalized arteriosclerosis with arteriosclerotic heart disease. Munger [7] reported a 38% incidence of cardiac disease in urologic patients, and this was an over-all study for all ages. Kretschmer [8] reported a few years ago before this association a clinical incidence of 35%. Lichtman and Master,[9] however, in a recent report of

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Dr. Edward J. Feyerer made the statistical review of the cases reported.

1. Young, H. H., and Davis, D. M.: Young's Practice of Urology, Philadelphia, W. B. Saunders Company, 1926, vol. 1.

2. Cabot, H.: Modern Urology in Original Contributions by American Authors, Philadelphia, Lea & Febiger, ed. 3, 1936, vol. 1, p. 708.

3. Swan, C. S., and Mintz, E. R.: Review of Prostatectomies for Benign Prostatic Hypertrophy at Massachusetts General Hospital in Years 1926-1930, Inclusive, J. Urol. **26**: 67-90, 1931.

4. Latchem, C. W., and Emmett, J. L.: Transurethral Resection for Men 80 or More Years of Age, J. Urol. **53**: 482-485, 1945.

5. Shivers, C. H. de T., and Groom, C. E.: Prolonged Morbidity Following Operation for Benign Prostatic Hyperplasia: Statistical Survey, J. Urol. **59**: 893-906, 1948.

6. Taylor, J. A., and Place, C. H.: Evaluation of Transurethral Prostatectomy, J. A. M. A. **139**: 144-146 (Jan. 15) 1949.

7. Munger, H. V., and Munger, A. D.: J. Urol. **64**: 41-48, 1950.

8. Kretschmer, H. L., and Butler, S.: Prostatic Surgery and Heart Disease, J. A. M. A. **136**: 441-444 (Feb. 14) 1948.

9. Lichtman, R. A., and Master, A. M.: Penicillin Prophylaxis of Postoperative Bacteremia and Bacterial Endocarditis, M. Ann. District of Columbia **19**: 663-673, 1950.

necropsy protocols in 406 consecutive cases of patients over 50 years of age reported an incidence of heart disease of 84%. It is interesting to note that 17% of their patients with negative findings on cardiac examinations proved at autopsy to have valvular involvement. It should be accepted, then, that heart disease is not always clinically demonstrable and that for all practical purposes the octogenarian has a cardiac condition and must be treated with respect to it. In the present series there was a clinical incidence of heart disease of 53%.

PREOPERATIVE CARE

When one is dealing with surgery in the aged, time should not be considered as an important factor. The average preoperative period of hospitalization in this series was 16½ days. Preoperative stabilization is most important, irrespective of time, and will often spell the difference between success and failure. One can realize from the associated conditions recorded in these aged patients that here is a place for good medical teamwork. The internist is a help in treating cardiac decompensation, diabetes, blood disorders, acidosis and other associated conditions.

Urologically, our problem is one of control of infection and of correction or stabilization of the blood urea level, particularly in cases of acute urinary retention, which occurred in 57% of this series. Use of an indwelling catheter, supplemented with infusions and/or hypodermoclyses, depending on the extent of cardiac disease, is standard therapy. It is agreed with Munger that glucose and oxygen are very essential for proper cardiac function. In some patients it is not possible to get the urea to a normal level, and these are operated upon when the urea level is stabilized. It is surprising how often the urea level becomes normal after urinary function is restored.

An illustrative case was that of J. C., admitted with acute urinary retention in 1947. He had a urea nitrogen level of 49 mg. per 100 ml., diabetes, cardiovascular disease, a dilated aorta, and an Escherichia coli infection of his blood stream. It took two months of preoperative care to bring him to surgery. At that time his urea nitrogen level was stabilized at 24 mg. per 100 ml. After the removal of 65 gm. of tissue his vesical function was restored on the third postoperative day. His urea nitrogen level promptly fell to normal, and he is alive and well, with a normal blood urea level and good vesical function today, at the age of 83.

Preoperatively, cultures of the urine are done routinely, and the proper antibiotic is selected for the offending organism, with sensitivity tests, if necessary. Antibiotics are used prophylactically in the cases without infection preoperatively and continued through the immediate postoperative period. In this way, infection, which is a troublesome factor, is kept to a minimum and the chances for bacteremia are lessened.

ANESTHESIA

In the first 21 cases in this series, prior to May, 1939, the operations were done with a combination of transsacral and caudal block, according to LeBat's method. At that time I [10] began using spinal anesthesia through a lumbosacral subarachnoid tap. This is given with the patient prone, which is not so exhausing to these elderly patients as is forced flexion. It is also given at the lowest possible level and therefore at the safest level. It is a relatively simpler procedure than a tap in the lumbar region. This procedure has been used almost exclusively since then, although a few operations have been done with intravenously given thiopental (pentothal®) sodium anesthesia. The science of anesthesiology has so advanced during the past years that anesthesia is not the concern it was when this series was begun, 19 years ago. A discussion of the relative merits of anesthesia in a symposium such as this should be left to the discussants. It has been my experience with these aged patients that preoperative sedation is not necessary and, when given, seems to enhance the likelihood of a drop in blood pressure. Oxygen is given routinely throughout the operation, with phenylephrine (neo-synephrine®) hydrochloride ready for any sudden fall in blood pressure. In this way these elderly patients stand anesthesia and operation quite well. Only one patient had what was considered cardiac failure during the operation, and he survived. It has been my experience that patients with coronary histories who are well over their accident and are stabilized stand operation well. I have had little trouble with patients known to have cardiac disease.

OPERATION

The objective in these cases is to remove as much prostatic tissue as possible and to restore vesical function. If for any reason, such as the size of gland or the patient's condition, this objective is not attainable, the operation is stopped and further resection is planned if vesical function is not restored. It is considered better judgment to stop the operation and repeat it rather than subject these poor risks to a prolonged procedure. It is my habit not to operate over an hour. It is also considered a mistake to allow these patients to leave the hospital with large amounts of residual urine, even if vesical function has been restored to their satisfaction.

A case in point is that of a 92-year-old man, admitted last November with benign hypertrophy, who had suddenly become unable to catheterize himself after having done this daily for 25 years. He had had an indwelling catheter for five weeks and could not urinate when it had been removed. He had a mixed infection with Proteus vulgaris and Aerobacter aerogenes and arteriosclerotic heart disease. At his first operation 79.5 gm. of tissue was removed; after he was afebrile, he voided well but had 13 oz. (390 cc.) of residual urine. On his 13th postoperative day a second resection (51 gm.) was done, for a total of 130.5 gm. He left the hospital two weeks later with restored vesical function and has remained well since. This was the largest amount of tissue removed in any of these cases. The average amount of tissue was 37.1 gm.

POSTOPERATIVE CARE

Postoperative care is maintained along the lines of general supportive therapy, with the replacement of blood loss, administration of dextrose intravenously for sustenance, proper hydration, and cardiac and general stimulants as required. Here again the internist is a great help in the cases of circulatory and ancillary conditions. Early ambulation is very important in these aged patients. Many of these patients are operated on in the afternoon and are allowed out of bed the next morning. Most of them have not been confined to bed for over two days throughout their hospital stay. The average postoperative stay in this series was 15.7 days. Here again

10. Taylor, J. A.: Lumbosacral Subarachnoid Tap, J. Urol. 43: 561-564, 1940.

time is not considered. Most of these patients have personal problems at home, often living alone, and having no one to care for them. They are often kept in our wards longer than necessary in order that they may be strong enough to meet these problems.

RESULTS

There is no hesitation in doing a second resection if required before the patient is discharged and this is explained to them beforehand, but it is my objective to do as complete a prostatectomy as is possible, in order that these elderly persons need not be subjected again to prostatic surgery. In spite of our best efforts, 4.8% were readmitted for further resection. Although there were no deaths in the first half of this series, which has already been reported, there have been four deaths in the last half, making an over-all total of 3.1%.

COMMENT

I began using the resectoscope in 1932 and used it cautiously in selected cases. As my experience and proficiency grew, it was used in more and more cases until during a few years in the latter part of the second decade of my practice it was used in practically all cases of prostatism. Eight years ago my thinking was modified to the extent that I believed the type of operation should be fitted to the patient and that no one operation was suitable for all patients with prostatic troubles. Since then, transurethral resection has been used in selected cases to which it seemed best adapted. It is believed that it is the ideal procedure for the aged because it is a surgical procedure with a minimal risk. It is a most difficult operation to teach, as it is a one-man procedure. A resident can be told what to do, but he cannot be supervised while he is doing it.

SUMMARY

With proper preoperative and postoperative care, transurethral resection done with the patient under spinal anesthesia at the lumbosacral level is the safest surgical approach to the prostate and is particularly suited to the aged prostatic patient. A review of 120 consecutive cases of patients between the ages of 80 and 96 substantiates this hypothesis.

2 E. 54th St.

OBSTETRIC HEMORRHAGE

Edward A. Schumann, M.D., Philadelphia

Twenty years ago the principal causes of maternal death were puerperal sepsis, toxemia, and hemorrhage in the order named, hemorrhage being by far the least frequently encountered cause of death. Now the situation has reversed; hemorrhage is the principal destroyer of maternal life, toxemia the second, while puerperal sepsis has been relegated almost to the limbo of forgotten diseases. This, of course, is due to the advent of chemotherapy and the antibiotics. The increasing ratio of hemorrhage as a lethal agent is both relative and absolute. Because the incidence of sepsis and toxemia has been reduced materially while the incidence of hemorrhage has not, there is a definite relative increase in the incidence of hemorrhage. Also, the use of prolonged analgesia and anesthesia unquestionally contributes to postpartum bleeding.

Bleeding of varying severity may occur at any time during pregnancy, labor, or the puerperium, and it is often associated with some defect in the implantation of the placenta, although there are many other sources.

The cause of bleeding during pregnancy varies with the period of gestation and for the purpose of diagnosis it is well to consider the three trimesters and to classify the causes of hemorrhage in each according to their relative frequency.

CAUSES OF HEMORRHAGE IN FIRST TRIMESTER

During the first three months by far the commonest cause of uterine bleeding is threatened or inevitable abortion. The second is threatened or inevitable abortion, and the third might be described in the same words. This repetitious statement is made in a somewhat childish endeavor to emphasize that abortion accounts for the vast majority of all cases of uterine bleeding during the first three months. The next most frequent cause is ectopic pregnancy, and other causes in decreasing order of frequency are hydatidiform mole, menstruation from one horn of a double uterus, uterine polyp, cervical erosion, and carcinoma, all of which are uncommon.

Although the classic symptoms of impending abortion are pain, hemorrhage, and dilatation of the os, it is quite common to have bleeding alone persist for days and even weeks before the other symptoms supervene. This condition, called threatened abortion, is sometimes puzzling and almost always causes a question as to appropriate treatment. In arriving at a diagnosis the first fact to be established is the pregnancy, which can be determined readily by a Friedman or frog test. Recent very interesting developments in cytology seem to indicate that the state of the embryo can be determined quite accurately by the relative preponderance of precornified or truly cornified cells in the vagina; it is probable that cytological means alone will enable the obstetrician to foretell whether the bleeding is associated with an embryo doomed to abort or whether there is a probability of salvaging it.

The hemorrhage in abortion may be furious, leading to the rapid exsanguination of the patient, and yet death from hemorrhage alone is an unusual occurrence. The management of abortion when it is merely threatened is, of course, an attempt to save fetal life; the patient is placed at rest with ice bags over the abdomen and morphine to relax uterine contractions. Diethylstilbestrol in fairly large dosage, 50 to 100 mg. daily, sometimes acts well. When the abortion is inevitable, as de-

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termined by the discovery of bits of decidua or a portion of the embryo in the discharge, complete evacuation by means of the curette and placental forceps is the method of choice, although there are a number of instances in which spontaneous miscarriage occurs with a fairly normal puerperium and without the necessity for curettage. Treatment is followed by the appropriate hematinics to restore blood loss.

In order to conserve space the use of blood transfusions in the obstetric hemorrhages will not be discussed in detail. It is sufficient to say that wherever there is bleeding, lost blood should be replaced by generous—and, if need be, repeated—transfusions, no matter what the origin of the hemorrhage. It is to be assumed, then, that transfusion is an essential part of the treatment of any of the types of hemorrhage under discussion.

In ectopic pregnancy bleeding is rarely profuse and does not take place until some hemorrhage has occurred about the embryo, which is either dead or seriously damaged. As a differential point the amount of bleeding is important, and the more visible blood there is, the more it is probable that the hemorrhage is due to an intrauterine abortion. It is also noteworthy that in ectopic pregnancy the amount of visible blood bears no relation to the clinical picture of the patient, since the massive hemorrhage, being intraperitoneal, is not disclosed to view. The common conception that ruptured ectopic pregnancy is associated with sudden catastrophic pain, fainting, and collapse, is true in slightly less than half of all cases, a slightly larger number presenting dull but increasing abdominal pain, rigidity of the rectus muscles, a slight elevation of temperature, and a moderate or high leucocytosis. Associated with these symptoms is vaginal bleeding, which, as has been said, is usually moderate or slight in amount.

The history of these cases is most important from a diagnostic standpoint. In abortion there is complete amenorrhea with the associated subjective signs of pregnancy, nausea and vomiting, polyuria, pain and tingling in breasts, and increased vaginal secretion. In ectopic pregnancy the signs of pregnancy are usually vague or at least not so pronounced as in uterine gestation. The amenorrhea is generally not complete, the patient stating that she had missed a period but noted some slight spotting a week or two later, which was repeated in greater amount before the onset of pain.

On bimanual examination the uterus in abortion is definitely increased in size and soft and globular in outline. The cervix is velvety and dilated to a varying extent. There may be some cyanosis of the cervical and vaginal mucosa, and Hegar's sign, obliteration of the lower uterine segment, may be present. Ladin's sign, a small area of marked softening in the anterior wall of the cervix and lower uterine segment, is a common finding. In ectopic pregnancy the uterus is generally only slightly enlarged and the characteristic boggy density is not noted. Movement of the cervix is often quite painful, and palpation of the adnexa may or may not reveal the presence of a tender, soft, spindle-shaped mass. If there has been a considerable accumulation of blood in the pelvic cavity, the cul-de-sac may bulge, with a doughy sensation being imparted to the examining finger.

The nature of the pain in the two conditions is often very valuable in diagnosis. In abortion the pain is intermittent and cramp-like, and the patient likens it either to menstrual cramps or to labor pains. In ectopic pregnancy the pain is at first to one side or the other of the midline, and then becomes a generalized abdominal ache as free blood in the peritoneal cavity causes irritation and mechanical peritonitis.

The management of abortion with severe hemorrhage is usually restricted to packing the vagina firmly with gauze or cotton under aseptic precautions, the packing to remain in place for 24 hours. Upon the removal of the gauze the products of conception often will be found lying free in the vagina. When the abortion occurs at the end of the third month or early in the fourth, the placenta often may be found lying in the cervical canal presenting as a tightly rolled cylinder; simple extraction with the fingers or a ring forceps under such a condition often stops the bleeding. The administration of ergot, especially the newer ergonovine preparations, will do much to contract the uterus and aid the extrusion of the ovum. Curettage is often not necessary, although it may be required in the presence of persistent bleeding.

The management of ectopic pregnancy requires little comment. Prompt laparotomy upon the establishment of the diagnosis is the rule. One point of importance is that in the interval between the occurrence of the hemorrhage and operation there should be no stimulation or intravenous therapy. Morphine to secure rest, elevation of the foot of the bed, and external heat are valuable measures, but stimulation should be reserved until the patient is prepared for section, when blood transfusion, 10% dextrose solution administered intravenously, and cardiac stimulants may be used freely.

Hydatidiform mole is a somewhat uncommon, but very definite, source of uterine hemorrhage. The diagnosis may be confirmed by the fact that the uterus is considerably larger than normal for the duration of the pregnancy, that the patient has experienced more than the ordinary degree of nausea and vomiting, that the Aschheim-Zondek or Friedman test is positive with greatly diluted urine (one-tenth of the usual amount), and that if the pregnancy is of more than 16 weeks' duration roentgenologic examination will fail to show centers of fetal ossification. The passage of the little cysts which constitute hydatidiform mole is conclusive evidence.

The treatment of a mole is immediate removal of the growth, possibly per vaginam, but better by abdominal hysterotomy under local anesthesia, the mole being removed under direct vision. It is almost unnecessary to say that all such cases should be watched closely with periodic Friedman tests to determine the possible signal of chorioepithelioma.

The other causes of bleeding during the first three months which I have mentioned are uncommon and may usually be recognized with ease by a speculum examination.

ABORTIONS IN SECOND TRIMESTER

In the second trimester abortions are still the leading cause of hemorrhage, closely followed as this period draws to a close by the bleeding from placenta praevia. Ectopic pregnancy, polyps, and other conditions previ-

ously mentioned may be responsible but not commonly so, since their presence usually has been disclosed earlier.

After the fifth month placenta praevia must always be uppermost in the mind of the obstetrician when uterine bleeding is present. The classic symptom is painless bleeding, often slight in amount at the first attack, with irregularly recurring hemorrhages of increasing severity. Since endometritis is an etiologic factor, a history of preceding abortions or uterine disease is of some value. The condition occurs far more commonly in multiparas than in primiparas, and the bleeding is always painless and seemingly without cause, although coitus or excessive muscular exercise may precipitate a hemorrhage.

The diagnosis of placenta praevia in the earlier months of pregnancy offers unusual difficulties. The bleeding is generally not excessive at this time, although, of course, there may be massive hemorrhage. Roentgenographic diagnosis has become increasingly important during the last few years, since the work of Snow and Powell in 1934 and Dippel and Brown in 1940 called attention to the value of soft tissue roentgenography. By this procedure the films are exposed with the patient in the lateral position, the location of the placenta becomes quite apparent, and, if the technical difficulties of x-ray study are overcome, the procedure gives a very accurate and definite picture.

Without roentgenological facilities the diagnosis must depend upon the history and nature of the bleeding and auscultation, with possible demonstration of a placental bruit low over the symphysis. The discovery upon vaginal examination of a soft, doughy mass lying between the head and the cervix will confirm the diagnosis, but this is a dangerous procedure and should not be done unless the accoucheur is prepared to deal at once with dangerous hemorrhage.

The treatment of placenta praevia constitutes one of the major problems of obstetrics, and the management of this lesion before the child is completely viable is a very perplexing one. However, there has been a tremendous change in the attitude of obstetricians toward placenta praevia in the past 10 years. The work of Herman Johnson of Houston, Texas, of C. H. G. MacAfee, and others has practically revolutionized our attitude toward the management of this condition. By applying the techniques suggested by these innovators, the maternal mortality has been reduced to well under 1% while the fetal wastage has been correspondingly lowered. The basis of the modern treatment may be stated extremely briefly as consisting of doing nothing and permitting the pregnancy to go on, induction of labor by rupture of the membranes, or Cesarean section. The choice of method depends upon the duration of the pregnancy, the amount of hemorrhage, and the condition of the cervix as to whether or not the membranes can be reached for puncture. The various procedures formerly in vogue, the use of dilating bags, Braxton-Hicks version, and so on, in general have been abandoned. Under the above plan of treatment the incidence of Cesarean section in placenta praevia will be about 40%. Obviously, whatever the treatment, blood transfusions should be resorted to early and often.

CAUSES OF HEMORRHAGE IN LAST TRIMESTER

In the last trimester of pregnancy abruptio placentae is one of the chief causes of uterine bleeding. Abruptio placentae, not nearly so frequent as placenta praevia, may possibly be due to trauma but far more generally is an expression of toxemia or even of some form of degeneration of the placenta itself. This accident, the concealed hemorrhage of the early writers, usually occurs during the last month of pregnancy and is associated with a usually moderate vaginal hemorrhage with evidences of serious internal bleeding. The accompanying symptoms of pain, shock in varying degree, rigidity of the uterus, and the absence of evidences of fetal life, are too well known to consider.

In this condition the important matter is the method of treatment, which is still somewhat controversial. In a paper just published, Hallenbeck and Williams strongly advocate Cesarean section in the severer cases. This was formerly my practice, but in more recent years more conservative tendencies have developed. In the majority of instances it would seem to be safer for the patient and viable infant to secure delivery from below by rupture of the membranes. However, if the hemorrhage and shock are severe and the cervix is still canalized and uneffected, Cesarean section after blood transfusion would seem to be the safer technique.

In those cases in which the uterine muscle fibers have been separated by the infiltration of blood and in which there is subperitoneal seepage (the Couvelaire uterus), the practice generally has been to do immediate hysterectomy. My experience leads me to believe that most of these uteri will recover if left intact, and my practice now is to retain them. Obviously the condition of the patient should govern the choice of methods used. If there is great blood loss which is possibly continuing within the uterine cavity, one cannot delay for the occurrence of spontaneous labor.

Ruptured uterus as a cause of obstetric hemorrhage needs but scant consideration. The symptoms which are so evident, the pain, the cessation of uterine contraction, and the rapidly developing internal hemorrhage, demand prompt surgical relief, generally by a hysterectomy.

After the delivery of the child, the obstetrician may be confronted with postpartum hemorrhage. Although many causes for this accident may be adduced, the commonest ones are atony of the uterus and retention of portions of placenta. It is an axiom in the clinics with which I have been associated that postpartum hemorrhage may be of two varieties: alarming but not dangerous and dangerous but not alarming.

By this is meant that the furious bleeding sometimes noted immediately after the birth of the child is intensely disturbing to the attendant but is usually managed immediately and definitely, whereas there are other patients in whom the bleeding is just a little more than normal, continues after the patient has been removed from the delivery room, and is noted by successive groups of house officers and nurses, none of whom feel that the bleeding is very marked until suddenly the patient rapidly goes into shock from continued blood loss.

So profound an impression did this type of hemorrhage make upon us that at the Kensington Hospital for Women there was a definite rule that a patient who bled

more than normally was attended by the same physician until the bleeding had ceased. In this way the blood loss could be estimated and treatment instituted.

The management of postpartum hemorrhage is also a subject of discussion. Cosgrove and his group in their large service practically never employ uterine packing, whereas at the Mayo Clinic Mussey recently discussed this question, strongly advocating the use of packing. My own convictions can be stated very briefly, namely, that the management of postpartum hemorrhage consists of haste, packing, and transfusion. By haste is meant promptly attacking the bleeding. By packing is meant completely filling the parturient uterus with an abundance of gauze packing. Then transfusion is given, of course. Should the patient bleed through the packing, it should be removed and replaced. Ergot by intramuscular or intravenous administration is a constant accompaniment of the treatment. Very rarely has it been necessary to perform hysterectomy for postpartum bleeding. Should the placenta on examination reveal any missing cotyledons, the uterus must be explored with a view to their removal.

Space does not permit a discussion of the management of retained or incarcerated placenta, although it must be stated that in those rare instances of placenta accreta in which manual removal is impossible the time-honored practice of hysterectomy is not necessary except in the event of profuse and continued hemorrhage. Expectant treatment with the free use of antibiotics usually results in a stormy convalescence with complete recovery after several weeks and the ability of the woman to bear children subsequently. Bleeding due to laceration of the cervix or perineum may be severe and even fatal. Careful inspection of the structures in the event that bleeding continues in the presence of a contracted uterus will reveal the injury, and the hemorrhage may be combated by suture.

1814 Spruce St.

PSYCHOTHERAPY IN PATHOLOGICAL DRINKING

Edward A. Strecker, M.D., Philadelphia

Within the time permitted it will be necessary to state conclusions somewhat positively without developing the premises on which the conclusions are based. I believe that the basic treatment of pathological drinking should be largely psychological and reeducational and not pharmacological. In my opinion the long list of drugs, to which tetraethylthiuramdisulfide (antabuse®) is a recent addition, has not made much treatment impress on alcoholism. If my hypothesis that pathological drinking is chiefly due to emotional immaturity dated in childhood is correct, then one would scarcely expect drugs to deal successfully with the issue, which is one of psychopathology rather than tissue damage. Incidentally, the use of tetraethylthiuramdisulfide is not without danger, perhaps particularly to the liver, and I have seen it produce severe psychotic reactions.[1] Briefly, I will divide my treatment concept into two subjects—psychological and reeducational conditions of treatment and physical adjuncts.

PSYCHOLOGICAL AND REEDUCATIONAL CONDITIONS OF TREATMENT

The patient must have some inner understanding of the need for help and some desire to obtain it. Patients who come for treatment under duress with the sword of some threat poised over their heads (perhaps the threat of a wife that she will divorce a husband unless he undergoes treatment or that of a father that he will disinherit his son) are not good candidates for therapy. Later on they may gain enough understanding so that the prognosis becomes better. The patient must be willing to try to remain abstinent during the treatment, but not by promises or pledges which are childish and usually unsuccessful. The patient, too, must be frank and honest in dealing with the therapist; for instance, he should notify him should a relapse occur. The conditions and circumstances of a relapse, analyzed by the patient and physician together, are very significant in the progress of therapy. In my series of rehabilitated patients, the number of relapses averaged a little more than three per patient.

The treatment proceeds by hourly consultation periods (at first several then about one a week) for about six months. The discussion material is largely at a conscious level, but, of course, many unconscious areas of psychopathology are penetrated. The bull's eye of therapy is the alcoholism, but many concentric circles come within the treatment range. In effect, the patient relives his life verbally, and often he comes to understand that his alcoholism is an adult escape mechanism motivated by the emotional immaturity produced in childhood by parental loving dominance, which left him illy equipped to deal with the problems of adult interpersonal relationships.

Sometimes, but not as often as the analysts believe, much deeper psychopathology, such as latent homosexuality, is uncovered. In my experience there is more often a latent heterosexuality—an aimless flitting about in the garden of love with an unconscious inability and unwillingness to accept the responsibilities of love life, home building, children and their rearing, and the many other aspects of true sexual maturity.

Since, as I believe, pathological drinking is a psychoneurosis, one encounters, as in other psychoneuroses, large segments of rationalization. These so-called "reasons" for drinking are often deceptively convincing, such as severe financial reversals or loss of a love object. As the alcoholism advances, the rationalizations become illogical and absurd—"my wife nags," "the children are noisy," "the weather is bad." These rationalized reasons

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1. Strecker, E. A., and Lathbury, V. T.: A Clinical Note on Antabuse, to be published.

for drinking are not the real reasons, and in the course of treatment the patient comes to understand and abandon these self-deceptions.

The controlling factor in therapy is the attitude of the therapist. It should be unemotional, impersonal, objective, not condoning, but still not critical or judging. This is all the more important since this attitude stands out in strong contrast to the environment in which the patient has lived previously—an environment in which he was carefully watched, praised or blamed, and rewarded or punished for sobriety or drunkenness as much as he was for good or bad behavior when he was a child. From the very first interview the therapist should decline to deal with the patient on anything but a mature basis, even though the mature segment of the patient's personality may be very fractional. For instance, when the patient says, "I suppose you won't let me have any liquor in the house" or ". . . serve cocktails to my friends" or ". . . go to the club" or ". . . stop at the taproom where I like to play darts" the answer is, "Do whatever you think best." It is amusing to note the disappointment of the patient at the refusal of the therapist to be authoritative and make such decisions for him.

Quite as important for the patient as his understanding of why he began to drink to excess is his gradual appreciation of why he now wants to stop drinking. His reasons for wanting to stop are sincere enough, but fallacious. The patient says he wants to be cured because he wants to bring some happiness to his old mother whose life he has made miserable, because he has disgraced his wife and children, and so forth. Such reasons are consciously valid, but actually and unconsciously they are merely sops to his belittled and shamed ego. There is just one reason why the patient wishes to attain sobriety. He must come to understand that it is for his own sake. It is a matter of survival, physical and mental. This is not to say that the remorse of the pathological drinker is not genuine. It is deep, poignant, and often excruciatingly agonizing. But the remorse serves no useful therapeutic purpose. Indeed, it often cannot be tolerated and leads the patient to drown out his sorrow and annihilate reality in a tidal wave of alcoholic debauch. It is the objective of the therapist to help the patient grow up emotionally, and an important facet of maturity is the facing of reality.

Among other things, the therapist should try to induce positive and negative thinking reflexes in the patient. He has been advised by family and friends to erase from his mind the painful remembrance of the repercussions of his alcoholic orgies. The therapist suggests that he do the opposite, remember them in all their horrible details, not with useless remorse but as experiences that need never be repeated. Conversely, it is suggested that he frequently review the many satisfactions of a nonalcoholic life.

The highest and most difficult hurdle for the patient to take is the acceptance of a nonalcoholic future. Even very intelligent patients find it very hard to relinquish the stubborn belief that they can drink moderately as other men do. I do not know why they cannot, but I do know they cannot. Actually, the pathological drinker is never cured. He remains well as long as he does not take alcohol of any kind in any amount. The patient cannot be ordered simply to take a nonalcoholic view of his future life. It is something he himself inculcates into his personality, and it emerges from the maturity-making relationship which exists between patient and therapist. When it is inculcated into the personality, it often becomes a very strong and irreversible conviction. It has been said that it is so firm that were the patient to depart this vale of tears and be welcomed at the heavenly gates by St. Peter proferring a cup of heavenly ambrosia he would automatically decline to taste, on the suspicion that it might contain alcohol.

So-called alcoholic dreams are interesting. In my experience, they are more likely to occur toward the end of treatment and are of a simple, wish-fulfilling type—a wedding, a lodge meeting, the union picnic, and other situations in which it would be natural to imbibe. The patient does take his dream drink and enjoys it. These dreams seem to represent last-ditch stands against abstinence, and I have found them to be of good prognostic omen.

I have reported merely the highlights of psychological therapy. All in all, it is a process of producing emotional growth which was denied in childhood. There are many details. I have found it useful not to direct but to suggest that each night the patient make out a list of the next day's activities. In such a schedule particular attention should be paid to times when there is likely to be alcoholic temptation. Departures from the schedule and the reasons for them should be discussed by patient and therapist.

It is still widely believed, and notably by families of patients, that change of occupation will solve the problem. It is a vain hope. There are no occupational dry docks. Sometimes, however, when the occupation is definitely above or below the capacity of the patient an occupational guidance test may lead to more satisfactory work in life.

To secure the cooperation of the family is far from an easy task. It is hard to convince an emotionally possessive mother that her plan of watching, following, protecting, bribing, and punishing her alcoholic son is not feasible. Some wives, however good their intent, are born to be sniffers. It is discouraging for someone who is sincerely trying to get well to be sniffed for the odor of alcohol as soon as he comes home. It is somewhat reminiscent of the mother who sniffs her baby to determine whether it is wet or dry. Nevertheless, no matter how difficult it may be, it is necessary for the therapist to secure a reasonable degree of understanding and cooperation from the family. The plant of therapy, which is being nurtured so that it will grow and flower into maturity, will wither and die if the home atmosphere continues to favor childish emotional dependency and immaturity in the patient.

PHYSICAL ADJUNCTS

I have not said anything about physical therapy. This does not mean that it is not an important adjunct. Since it is so obvious, it is scarcely necessary to state that the patient should be brought to his physical optimum. Usually a large intake of vitamins is indicated. The question of hospital or sanitarium care must be considered. In my experience about one out of every three patients needs such care because of physical depletion and in order to protect him when the desire for alcohol is over-

whelming. The shorter the period of hospital stay the better. There is danger that the hospital may become a womb of bricks and mortar, protecting the patient against facing reality. All in all, pathological drinking must be vanquished on the terrain of the ordinary, everyday life of the drinker.

The food habits of the alcoholic need close attention. Usually too little food is taken and often during debauches none at all. At best, scattered bites of food are taken during the day with perhaps a hot, heavy, indigestible dinner late at night. In some patients it is advisable to determine blood sugar levels, and when there are low levels, often late in the morning and afternoon, it is suggested that the patient eat some cookies or a bar of candy. There are many areas of physical therapy I have not discussed, since I do not think these are within the agenda of this report.

I have indicated that the attitude of the therapist should be mature, nonemotional, and objective, but much understanding and humility are needed. As he deals with alcoholic patients, in all sincerity the therapist should be able to say to himself, "There but for the grace of God go I."

111 N. 49th St.

ANTIBACTERIAL THERAPY IN INFECTIONS RESULTING FROM HUMAN BITES

REVIEW OF TWENTY-SEVEN CASES, WITH REPORT OF FOUR CASES IN WHICH BACITRACIN WAS ADMINISTERED

Irving A. Levin, M.D.
and
Alfred B. Longacre, M.D., New Orleans

Specific antibacterial therapy probably has contributed more to relieving the fear of previously serious infections than any other single development in recent years. Infections resulting from human bites were very serious prior to specific antibacterial therapy; the prognosis was poor and crippling resulted often. Many factors, including antibacterial therapy, are responsible for the improved results in the treatment of such infections.

The cases presented in this paper are those collected at the Charity Hospital of Louisiana in New Orleans, in which treatment was given during the year 1948-1949. Included in these cases are those of four patients who received bacitracin parenterally for an already-established infection. In separate papers Boyce [1] has presented two series of cases of infections resulting from human bites. These cases were collected from the records at Charity Hospital, New Orleans, and occurred prior to the cases reported in this paper.

A review of the literature does not give a very accurate bacteriological or etiological classification or description of the flora in this type of infection. In addition to aerobic bacteria, the mouth often contains anaerobic species of streptococci as well as the fusiform bacilli and spirochetes. The bacteria of the skin of the recipient of a human bite vary also, depending entirely on the flora transiently present when the wound is incurred. These infections almost without exception are mixed infections in which many or all of the bacteria recovered play a part. In addition to the individual action of these bacteria, there is undoubtedly a symbiotic relationship, which augments or is responsible for some of the characteristics of these infections. Among the anaerobic bacteria, probably the anaerobic streptococci are the most significant. However, occasionally these infections contain pathogenic Actinomycetes, and more frequently fusiform bacilli and spirochetes. It is our opinon that all the organisms probably are significant, particularly when we consider a symbiosis or synergistic action which these bacteria may exert upon each other.

Human bites occur most frequently on the dorsum of the hand and are incurred when the closed fist strikes the teeth of an opponent in a physical altercation. However, this is not the only location where these injuries have occurred, for they have resulted from a deliberate bite by an assailant on other parts of the body. The latter type of injury is seen most frequently in institutions where persons with mental diseases are treated.

The intelligent therapy of infections resulting from human bites and similar wounds requires a detailed knowledge of the tissue planes and anatomical structures involved. The spread of the infection will depend a great deal upon which tissue planes were contaminated at the time of the injury, for it is in these planes that the infection spreads. Mason and Koch [2] clearly demonstrated on cadavers the usual and expected route of the spread of these infections. There have been previous reports in which these infections were of such fulminating nature that at times they spread without apparent regard for the tissue boundaries.

SIGNS AND SYMPTOMS

The external characteristics of these injuries are so misleading that the patient often will neglect them until the characteristic signs of inflammation have occurred. The initial swelling and pain often are attributed to the

From the Antibiotic Research Laboratory, Louisiana State University School of Medicine.
Instructor in Surgery (Dr. Levin) and Assistant Clinical Professor of Surgery (Dr. Longacre), Louisiana State University School of Medicine.

1. (*a*) Boyce, F. F.: Human Bites: Analysis of 90 (Chiefly Delayed and Late) Cases from Charity Hospital of Louisiana at New Orleans, South. M. J. **35**: 631-638, 1942; (*b*) Human Bites: Study of Second Series of 93 (Chiefly Delayed and Late) Cases from Charity Hospital of Louisiana at New Orleans, South. Surgeon **14**: 690-708, 1948.

2. Mason, M. L., and Koch, S. L.: Human Bite Infections of Hand, with Study of Routes of Infection from Dorsum of Hand, Surg., Gynec. & Obst. **51**: 591-625, 1930.

contusion, of which the patient may or may not be aware. However, in those cases in which infections do occur, a dull aching pain associated with movement rapidly changes to a throbbing continuous pain. The swelling also increases and extends over the dorsum of the hand or the region of the injury. Since several hours usually elapse before this change occurs, there is usually a delay in seeking medical attention.

The appearance of the puncture wound usually does not change; in most cases the wound is dry and sealed with fibrin. The point of entry of the wound usually does not drain until the infection has been well established and the fibrous plug has been removed or extruded; drainage may be minimal for a long period. At the onset of the infectious stage the swelling, pain, and redness will continue in a proximal and distal direction. The drainage, when it does occur from the point of entry, is usually a foul-smelling, cloudy, purulent fluid, not as thick as in the usual pyogenic infection. Palpation at this stage usually demonstrates an edematous area without a definite wall of localization and without abscess formation. There is usually a slight systemic reaction characterized by malaise associated with the pain and infection. The febrile reaction is not very marked at first; the temperature is usually between 99 and 101 F. Later, as the infection progresses, the temperature may rise and the patient may become toxic.

REVIEW OF CASES

The 27 patients in the series reported here were treated in one of the various surgical services at the Charity Hospital in New Orleans. These cases have not been reported previously and were not included in either of the series reported by Boyce.[1]

Except for the incidence, the seriousness of these infections could not be correlated with the age, the sex or the race. These infections do occur most frequently in the age group comprised of those persons who are most likely to become involved in physical altercations, including the adolescents, young adults, and persons in the later part of the fifth decade of life. However, they can occur at any age, for the infection is the result of injury.

Since the average time lapse between the incurrence of the injury and the presentation of the patient for medical attention was five days, it might be considered that this series consists of late cases. The earliest case observed was that of a patient seen within 24 hours of the time the injury occurred, while one patient did not seek medical attention until 28 days following the injury. In most instances the patients would not present themselves until home remedies had failed to check the pain or the infectious process.

Anatomical distribution of the lesions corresponds to the distribution in the two series reported previously. In 11 instances the wound was on the dorsum of the hand just over the metacarpal-phalangeal joints. In eight other cases the point of entry was on the digits, and in single instances on the palm and various other parts of the body. All the patients were hospitalized and the average duration of the hospitalization was five or six days, the shortest being two days, and the longest continuing twelve days.

The present series contains 27 cases. A sulfonamide or one of the antibiotics was used as the specific form of antibacterial therapy in these cases. In twelve instances penicillin in combination with sulfadiazine was the therapy used; in four cases bacitracin was the only antibiotic, while in other individual cases either penicillin alone, penicillin and streptomycin in combination, penicillin, streptomycin, and sulfadiazine, or other combinations of these drugs were used. The results in these cases were very good in that the average hospital stay was approximately five days. The temperatures, which had ranged between 98.6 and approximately 101 F. on admission, returned to normal within four days after the treatments were begun. There was only one major complication and that occurred in a case in which osteomyelitis developed. The other complications occurred in three cases in which there was a residual limitation of motion in the involved fingers.

Bacitracin was the only new antibiotic used in this series of human bite infections. Treatment with bacitracin was successful in four cases.

REPORT OF CASES

Case 1.—A 36-year-old Negro man was admitted to the hospital one and one-half days after a hand had been lacerated by a human bite. There was moderate swelling of the dorsum of the hand, with marked tenderness, particularly in the region of the laceration. The laceration was reopened, and small bits of necrotic tissue were removed. Bacitracin was administered intramuscularly in doses of 11,800 units every six hours for two days; the daily dose was thus 47,200 units and the total dose 94,400 units in all. Within 24 hours the tenderness had disappeared completely and the swelling had partially disappeared also. The patient was then discharged.

Case 2.—A 54-year-old Negro woman was admitted with a human bite on the right forearm incurred 24 hours previously. She was suffering from chills and fever. The arm was markedly swollen and edematous. A moderate amount of foul-smelling fluid was draining from a laceration of the volar surface of the arm. Erythema extended 3 inches (7.62 cm.) around this laceration. The axillary nodes were swollen and tender, but there was no definite lymphangiitis. Intramuscular administration of bacitracin in doses of 5,000 units every six hours was started immediately; other treatment consisted of continuous warm compresses. The dose of bacitracin was increased to 10,000 units every six hours on the second day, and in the next 48 hours the edema had disappeared completely. Drainage from the wound had lessened, and the temperature had decreased. The patient was discharged on the fifth day with a small residual drainage for the treatment in the outpatient department. In this case no surgical drainage was necessary to control the infection.

Case 3.—An 18-year-old Negro man was admitted with a laceration on the left hand between the fourth and fifth metacarpal-phalangeal joints. The laceration had been incurred by striking the mouth of an opponent. Within 24 hours the hand became very swollen and the laceration began to exude a foul-smelling discharge. Examination on admission revealed a severe cellulitis on the dorsum of the hand and a ½ inch (1.27 cm.) laceration over the fifth metacarpal-phalangeal joint. The patient was treated with warm compresses and bacitracin in doses of 5,000 units every six hours, receiving a total dose of 40,000 units. Within 24 hours after admission there was a marked decrease of edema and pain, and within 48 hours all edema was gone. The patient was discharged on the third day, completely well.

Case 4.—This patient had an infection on soft tissues of the chest wall as a result of a direct human bite. The patient also had an infection resulting from a human bite on the distal phalynx of the index finger. Intramuscular bacitracin therapy was started, and no surgery was performed. Within 24 hours almost all the tenderness and pain associated with both of the lesions had subsided completely. The patient was discharged on the fourth day after treatment was begun, with both lesions healed.

COMMENT

Since the usual course of infections resulting from human bites is so bad without antibacterial therapy, the dramatic results obtained in these four cases suggest that bacitracin played a significant, if not major, role in the successful outcome.

The antibacterial spectrum of bacitracin includes most species of the organisms affected by penicillin but also includes strains of species that are not affected by penicillin. Clinically, bacitracin seems to be more effective than the other antibiotics against the anaerobic flora of Streptococcus. Since the exact role of the spirochetes and fusiform bacilli of the mouth in these infections is not clearly understood, any form of therapy must also be directed at these organisms.

Boyce [1] collected 190 cases from the records of Charity Hospital in New Orleans in which treatment was given during the period 1921-1941, the preantibiotic era. In the latter part of this series there were a few cases in which one or another of the sulfonamide drugs was used, but the number of these cases and the treatment given do not warrant a comparison with those in which a sulfonamide was not given. Therefore the greater morbidity in this group of cases is attested to by several points: the prolonged hospital stay, the higher incidence of surgical drainage, and the much higher incidence of serious complications. Complete amputation of digits was required in 21 instances, partial amputation of digits in three, and ostectomy in three others. In addition, one amputation of an arm had to be performed, and there was one death due to pneumonia.

The cases reported by Boyce [1b] in the second paper were collected from the period 1941-1948. All of these patients received at least one of the newer antibacterial therapeutic agents, and in many instances they received a combination of antibacterial drugs. For the most part the drugs were penicillin, sulfadiazine, streptomycin, and combinations of these drugs. Except for the use of specific antibacterial therapy, the treatments in these cases generally paralleled the treatments in the preceding series. In this group there were no deaths, and in only three instances was it necessary to perform a mutilating operation. In many instances the inflammatory reaction subsided without surgical intervention. Boyce credits specific antibacterial therapy with being responsible, or a major factor, in obtaining these improved results.

Meleney,[3] in a report of the use of bacitracin in the local treatment of surgical infections, clearly demonstrated that this antibiotic has definite therapeutic value. In a subsequent paper discussing the parenteral use of bacitracin in the treatment of surgical infections, Meleney [4] collected enough cases to evaluate the effectiveness of this antibiotic. The good results in infections caused by the Gram-positive cocci as well as in other infections demonstrated that bacitracin has definite therapeutic value. Treatment with bacitracin after other agents had failed resulted in a cure in a high percentage of these cases. Longacre and Waters [5] have reported their experiences in administering parenteral bacitracin in the treatment of 50 consecutive cases of various surgical infections. In this study they found that the therapeutic result was excellent in 60, or 70% of the cases, and in only a very small percentage was there no beneficial effect with bacitracin. Bacterial studies correlated with study of the flora obtained from these as well as other species and strains of bacteria have outlined the bacterial spectrum of the antibiotic action of bacitracin. In a very rough or gross manner bacitracin has definite bacterial action against most Gram-positive cocci, many of the Gram-positive bacilli, and some of the spirochetes and fusiform bacilli.

It can be said that, except in very high concentrations, bacitracin does not have any antibiotic action against most of the Gram-negative bacilli. This is important, because with patients requiring systemic or parenteral administration of bacitracin one cannot hope to attain a sufficient concentration to modify an infection in which the Gram-negative bacilli play a major role. However, in the laboratory it has been demonstrated that bacitracin in concentrations of 300 to 500 units per gram or cubic centimeter will inhibit many of the Gram-negative bacilli. Bacitracin can be applied locally in these concentrations, and therefore in local treatment it may be effective against a group of Gram-negative organisms. Bacitracin is as effective against the anaerobic group of organisms as other antibiotics available at the present time. Consequently, it can be concluded that, from a purely antibiotic action, bacitracin should be of value in inhibiting the growth of organisms responsible for many surgical infections, including those caused by the mouth flora.

The excellent therapeutic result obtained in the four cases reported in this paper suggest that bacitracin should be the antibiotic of choice in the treatment of infections resulting from human bites. It will be noted that in the four cases reported there were no toxic reactions and the drug was therefore safely used under the conditions. In infections caused by the human bite which are fulminating in nature and which will almost invariably result in disfiguring operations bacitracin by the parenteral route is definitely indicated to obtain the desired therapeutic results. It is felt that the therapeutic value outweighs the risk of an untoward toxic manifestation. However, in infections resulting from human bites which are not fulminating, it is within the realm of rational antibiotic therapy to use penicillin, which has also been demonstrated to be very effective in controling these infections.

CONCLUSIONS

A series of 27 additional cases of infections resulting from human bites which were treated at the Charity Hospital in New Orleans is presented. The results in the collected series, two by Boyce and one presented in this paper, are discussed. A marked improvement in the therapeutic results following the introduction of specific antibacterial therapy is reported. This improvement began with the sulfonamides, became greater with the introduction of penicillin, and the four cases presented, in which bacitracin was used, suggest that even further improvement may be hoped for when bacitracin becomes available for more general use.

3. Meleney, F. L., and Johnson, B.: Bacitracin Therapy: First 100 Cases of Surgical Infections Treated Locally with Antibiotic, J. A. M. A. **133**: 675-680 (March 8) 1947.

4. Meleney, F. L.; Altemeier, W. A.; Longacre, A. B.; Pulaski, E. J., and Zintel, H. A.: Results of Systemic Administration of Antibiotic, Bacitracin, in Surgical Infections: Preliminary Report, Ann. Surg. **128**: 714-731, 1948.

5. Longacre, A. B., and Waters, R. M.: Parenteral Bacitracin in Surgical Infections, Am. J. Surg. **81**: 599-606, 1951.

REACTIONS TO INTRATHECAL STREPTOMYCIN

R. James McKay Jr., M.D., Burlington, Vt., John A. V. Davies, M.D., William Berenberg, M.D., Boston
and
Harry M. Lowd Jr., M.D., Salem, Mass.

In 1946 Cairns, Duthie, and Smith [1] reported the occurrence of serious toxic reactions to intrathecal streptomycin in a group of patients under treatment for meningitis. They observed four such reactions among the seven patients studied. The symptoms occurred from a few minutes up to nine hours after intrathecal injection. Two cases terminated fatally at a time when death was not expected by those in attendance. Both fatalities followed intrathecal doses of 100 mg. of streptomycin. Two other reactions classified as very severe occurred after doses of 80 mg. and 2.5 mg. respectively. The symptoms observed consisted of coma with disturbances of temperature, pulse, and respiration. Respiratory failure was the mode of death in the two patients who died. Valergakis, Hays and Sutherland [2] have recently reported two patients with similar reactions to the intracisternal administration of streptomycin. One of these reactions was fatal.

Because of a dearth of such reports in the American literature and because of the still popular concept,[3] despite evidence to the contrary,[4] that the use of intrathecal streptomycin in certain types of meningitis is both necessary and harmless to the patient, it seems worthwhile to report our experience with it. With one exception (Case 8 was treated at Salem Hospital, Salem, Mass.) the clinical material from which the cases for this report were drawn consisted of 65 consecutive patients with Hemophilus influenzae meningitis and 25 patients with tuberculous meningitis, all of whom received repeated intrathecal injections of streptomycin (Table). Unfortunately, no record was made of the drug lot numbers used in any case. The group with meningitis due to H. influenzae was admitted between November, 1945 and July, 1948. Since that time we have discontinued the intrathecal administration of streptomycin in treating this disease. The therapeutic results, which have been excellent, will be reported elsewhere.[5] The patients with tuberculous meningitis were treated between December, 1946, and September, 1949.

In order to illustrate the type of reaction encountered and its relation to the outcome of therapy, the following brief histories of eight patients treated with intrathecal streptomycin for meningitis, proved by culture to be due to H. influenzae, Type B, are presented. Additional data are supplied in the accompanying table. Cases of H. influenzae meningitis were chosen for more detailed illustrative purposes because of better evidence that intrathecal streptomycin is unnecessary in the treatment of this disease, as compared with tuberculous meningitis. Also because of the better prognosis in the former disease—i. e., there were no deaths among the last 55 consecutive patients treated for it at Children's Medical Center—a fatal reaction to intrathecal medication presumably means the loss of a patient who otherwise would probably have survived.

The routine practice in this institution is to allow cerebrospinal fluid to flow from the needle until the pressure reaches a normal level and then to inject very slowly with a syringe, using very slight pressure, the streptomycin dissolved in isotonic sodium chloride solution, in an amount somewhat less than the volume of fluid withdrawn.

REPORT OF CASES

CASE 1.—M. V., a 7-month-old white girl was moderately ill on admission with a four-day history suggestive of meningitis.

During the first seven days in the hospital she received 300 mg. of antiserum intravenously and sulfadiazine, without significant alteration in her condition. Intrathecal injection of 20 mg. of streptomycin on the eighth day was followed 15 minutes later by slow, labored respirations and cyanosis of short duration. The cerebrospinal fluid culture was negative for the first time 24 hours later and remained so for the rest of her course. Nine out of 11 subsequent intrathecal injections of the same amount of streptomycin were followed by temperature rises of two to four degrees F for periods of four to eight hours.

CASE 2.—L. H., a one-year-old white boy, was critically ill on admission, with a 24-hour history suggestive of meningitis. He received his first intrathecal injection of 100 mg. of streptomycin shortly after entry. Culture of his cerebrospinal fluid, initially positive for H. influenzae, Type B, was negative 12 hours later and remained so thereafter. Immediately after the second intrathecal dose of 100 mg. he had a series of clonic convulsions, having had only rather mild tonic convulsions until that time. Because of this the intrathecal dose was reduced to 50 mg. Cultures continued negative, and the patient improved slowly until the fourth hospital day when he went into coma and peripheral vascular collapse with slow, irregular respirations and periods of apnea up to 10 seconds in length. This occurred without warning six and one-half hours after his seventh intrathecal injection of streptomycin. Ventricular and lumbar taps revealed no increase in pressure at either site. He gradually improved over a period of about one hour. He received seven more intrathecal injections without untoward symptoms.

CASE 3.—R. D., a 10-week-old white girl, was severely ill on admission 12 hours after onset of her disease. Cerebrospinal fluid sugar was 43 mg. per 100 cc. but the peripheral white blood cell count was only 3,000 on entry. She showed marked clinical improvement during the first 12 hours in the hospital, although her cerebrospinal fluid culture remained positive. She ate well, seemed in excellent condition, and a good prognosis was entertained. Thirteen hours after her first intrathecal dose of 50 mg. of streptomycin she received 100 mg. in 20 cc. of isotonic sodium

Dr. McKay is now affiliated with Mary Fletcher Hospital, Burlington, Vt., and Dr. Lowd with Salem Hospital, Salem, Mass.
From the Department of Pediatrics, Harvard Medical School and the Department of Medicine, Children's Medical Center, Boston.

1. Cairns, H.; Duthie, E. S., and Smith, H. V.: Intrathecal Streptomycin in Meningitis: Clinical Trial in Tuberculous, Coliform and Other Infections, Lancet **2**: 153 (Aug. 3) 1946.

2. Valergakis, F. E. G.; Hays, D. S., and Sutherland, A. M.: Reactions Following Intracisternal Use of Streptomycin, J. A. M. A. **142**: 720 (March 11) 1950.

3. (*a*) Dowling, H. F.; Sweet, L. K.; Hirsh, H. L., and Lepper, M. H.: Specific Therapy of Bacterial Infections of the Central Nervous System, J. A. M. A. **139**: 755 (March 19) 1949. (*b*) Crook, W. G.; Clanton, B. R., and Hodes, H. L.: Hemophilus Influenzae Meningitis: Observations on the Treatment of 110 Cases, Pediatrics **4**: 643 (Nov.) 1949.

4. (*a*) Cairns, Duthie, and Smith.[1] (*b*) Valergakis, Hays, and Sutherland.[2] (*c*) Hoyne, A. L., and Brown, R. N.: Intrathecal Therapy Not Required for H. Influenzae Meningitis: A Report of 28 Cases, J. A. M. A. **136**: 597 (Feb. 28) 1948. Wilson, G.; Rupp, C., and Wilson, W. W.: The Dangers of Intrathecal Medication, ibid. **140**: 1076 (July 30) 1949.

5. McKay, R. J., Jr.; Davies, J. A. V., and Winter, W. D., Jr.: Treatment of Hemophilus Influenzae Meningitis Without Intrathecal Therapy, to be published.

chloride solution after withdrawal of 25 cc. of cerebrospinal fluid. One hour later she suddenly developed peripheral circulatory failure, with slow, irregular respirations and long periods of apnea. Her anterior fontanel was flat, as it had been at the time of the lumbar tap. Her condition remained unchanged, and she died eight hours after the last intrathecal injection. Post-mortem examination showed no evidence of a pressure cone or other explanation for her unexpected death. Cultures of blood, brain, and cerebrospinal fluid were all negative at post-mortem examination.

CASE 4.—B. V., a 13-month-old white boy, was severely ill but well oriented and responsive when admitted 60 hours after the apparent onset of his disease. The period following his first intrathecal dose of 100 mg. of streptomycin was uneventful. His condition was satisfactory in the period just preceding his second 100 mg. intrathecal dose, which was given 11 hours after the first, and cerebrospinal fluid cultures taken at this time were negative. Immediately after the second intrathecal injection was completed he started to twitch occasionally for the first time during his illness. One and one-half hours later he was completely unresponsive and breathing with slow, gasping respirations. Five hours after completion of the injection he twitched almost continually, developed periods of apnea, and perspired profusely. His temperature rose from 103.6 F. to 108 F. He showed some improvement during the next seven hours and his temperature fell to 103.4 F. At this time he received a third intrathecal dose of 100 mg. of streptomycin in 10 cc. of isotonic sodium chloride solution. Seven hours later his temperature had risen to 108.2 F. He remained completely unresponsive and died 14 hours after the third intrathecal injection. Cerebrospinal fluid cultures had been negative since the beginning of treatment. Post-mortem examination showed thick subarachnoid exudate and some pneumonia. Cultures were negative.

CASE 5.—J. G., a 17-month-old white girl, was critically ill on admission 24 hours after onset of her disease. She responded well to treatment, including intrathecal injections containing 50 mg. of streptomycin twice daily. Cerebrospinal fluid cultures were negative 14 hours after the beginning of treatment and remained so thereafter. She had shown great improvement and had been afebrile for 36 hours at the time of her eighth intrathecal injection when she suffered a mild vasomotor collapse shortly after withdrawal of the needle. Cerebrospinal fluid pressure was not elevated at the time of the lumbar puncture. Recovery was rapid, and she had no further difficulty despite two more intrathecal injections given at 24-hour intervals.

CASE 6.—C. M., a 10-week-old white girl, was critically ill on admission after 60 hours of illness during which she received only sulfadiazine. There was poor clinical response to treatment with high doses of intramuscular streptomycin and two intrathecal injections of 100 mg. of streptomycin, although all cerebrospinal fluid cultures, including the post-mortem cultures, were negative after 17 hours. Six hours after the second intrathecal dose she suddenly became cyanotic, with gasping respirations, but improved gradually during the next six hours and seemed to be holding her own. She received another intrathecal injection of 50 mg. of streptomycin at this time. Nine hours later she died suddenly and unexpectedly, 42 hours after admission. Post-mortem examination showed several small areas of cortical hemorrhage and softening, subarachnoid hemorrhage over the pons and medulla, and thrombosis of the left posterior inferior cerebellar vein, as well as of a number of smaller vessels. There was also microscopic evidence of pneumonia in the posterior portions of both lower lobes.

Reactions to Intrathecal Streptomycin

Case	Patient	Age	Type of Meningitis	Dose Causing Reaction	Size of Dose	Time Interval Between Dose and Reaction	Severity	Symptoms	Date
1	M. V.	7 mo.	H. Influenzae	1 2, 3, 4, 5, 6, 7, 8, 9, 12	20 mg. 20 mg.	15 min. 2-4 hr.	Severe Mild	Cyanosis, slow respirations Temperature rise of 2-4 degrees F.	November 1945
2	L. H.	1 yr.	H. Influenzae	2 7	100 mg. 50 mg.	Immediate 6½ hr.	Moderate Very severe	Convulsions Coma, shock, apnea	July 1946
3	R. D.	10 wk.	H. Influenzae	2	100 mg.	1 hr.	Fatal	Coma, shock, apnea	August 1946
4	B. V.	13 mo.	H. Influenzae	2	100 mg.	Immediate	Fatal	Convulsions, coma, gasping respirations, temperature rise	August 1946
				3	100 mg.	7 hr.	.....	Temperature rise	
5	J. G.	17 mo.	H. Influenzae	8	50 mg.	15 min.	Moderate	Shock	September 1946
6	C. M.	10 wk.	H. Influenzae	2	100 mg.	6 hr.	Very severe	Cyanosis, gasping respirations	April 1947
7	J. W.	10 mo.	H. Influenzae	1	50 mg.	2 hr.	Severe	Shock, slow respirations	June 1947
8	D. D.	4 mo.	H. Influenzae	4	25 mg.	½ hr.	Fatal	Shock, coma, convulsions, labored respirations, temperature rise	April 1948
9	D. C.	5 yr.	Tuberculous	2	50 mg.*	5 hr.	Moderate	Cerebellar signs	December 1947
10	M. M.	1 yr.	Tuberculous	1, 2, 14	50 mg.	1 hr.	Very severe	Pallor, coma, vomiting, transverse myelitis	May 1948
11	L. L.	10 mo.	Tuberculous	3	50 mg.	5 hr.	Fatal †	Pallor, vomiting, irregular respirations	July 1949
12	R. T.	2 mo.	Tuberculous	14	50 mg.	6 hr.	Fatal †	Coma, slow, irregular respirations	July 1949
13	K. A.	2 yr., 9 mo.	Tuberculous	20	50 mg.	4 hr.	Severe	Vomiting, lethargy, cyanosis, cerebellar signs	August 1949
14	F. B.	2 yr., 10 mo.	Tuberculous	48	50 mg.	3 hr.	Severe	Cerebellar signs, vomiting, pallor, stupor, temperature rise	August 1949

* By intravenous route.
† The patients in Cases 11 and 12 were so ill at the time of injection that, although we are reasonably sure they died from it, intrathecal streptomycin can be considered only a possible cause of their deaths.

CASE 7.—J. W., a 10-month-old white boy, was severely ill on admission after 48 hours of illness. Two hours after his first intrathecal injection of 50 mg. of streptomycin he suddenly went into shock, with ashen color and slow respirations. He improved within an hour and had no more difficulty after receiving seven subsequent intrathecal injections of the same amount of streptomycin.

CASE 8.—D. D., a 4-month-old girl was severely ill at the start of treatment 24 hours after onset of meningitis. In addition to other therapy she received 25 mg. of streptomycin in 10 cc. of isotonic sodium chloride solution twice daily and showed marked improvement in every way, with negative cerebrospinal fluid cultures 24 hours after the start of treatment. She continued to improve, and her prognosis was considered to be excellent until half an hour after her fourth intrathecal injection, when she became extremely pale, with labored respirations. Two hours later her temperature had risen from 101 to 107.6 F. and she had generalized convulsions for the first time. Her condition did not improve and she died six hours after the intrathecal injection. Post-mortem examination revealed a horseshoe kidney, bicornate uterus, common urethrovaginal orifice, and enlarged clitoris. Other findings showed no abnormality. There was no evidence of a pressure cone, and cultures were negative.

To summarize, the type of reaction seen consisted of vasomotor collapse with respiratory irregularity and temporary inability to handle upper respiratory tract secretions adequately during the period of reaction, the use of suction being necessary in most of the patients to clear the airway. The onset was within an hour of the intrathecal injection in half the patients and between two and six hours in the remainder. If the duration of the reaction was more than one hour, the peak was not reached, regardless of time of onset, until five to nine hours after the patient received the dose of intrathecal streptomycin. All patients appeared to be in imminent danger of death during the period of reaction. Convulsions occurred in three children, and a marked rise in body temperature was observed in four. Both convulsions and hyperpyrexia occurred in two patients whose deaths were attributed to the intrathecal medication. Vomiting was observed in four children, transverse myelitis in one. Six of the 14 patients died within 20 hours after an intrathecal injection of streptomycin, although only three deaths seemed clearly attributable to it. In Case 6, the patient did have a characteristic reaction following her second intrathecal dose, although death was probably caused by other factors. In Cases 11 and 12 death did not occur until 18 and 20 hours, respectively, after the intrathecal medication. Both patients were extremely ill at the time the drug was administered. However, a sudden, rapid, unexpected change for the worse occurred in both infants following intrathecal medication, and they went steadily downhill and died within 24 hours. No fatal reactions occurred after the first intrathecal dose, and all deaths occurred in infants 13 months of age or younger. Autopsies were performed on all children who died. Only in Case 6 was an explanation found for the sudden deterioration of the patient's clinical condition. There was no pressure cone at the base of the brain in any of the patients, nor was there any evidence of meningeal irritation or adhesions that could be attributed to intrathecal medication. Intracranial hemorrhage and thromboses of cerebral blood vessels were observed only in Case 6. Areas of cortical necrosis were not found in any of the patients autopsied.

Because symptoms of shock and vasomotor collapse have also been observed in patients with meningitis who did not receive intrathecal streptomycin, it was important to analyze our data further. In the total group of 65 patients receiving intrathecal treatment for meningitis due to H. influenzae only six were given doses of more than 50 mg. Four of them have been reported above. Of the remaining two patients, one received 100 mg. only in her first injection. The second had severe, known hydrocephalus at the time she contracted meningitis, and hence might not be expected to build up very high concentrations of streptomycin in the cerebrospinal fluid, even after repeated large doses. A comparison between the incidence of the type of reaction described in the patients (four out of six) receiving intrathecal doses of 100 mg. of streptomycin and the incidence among those who received smaller intrathecal doses (three out of 59), shows the great improbability ($P<.01$) that this occurred by chance.

Because of the definite relation of this type of reaction to the size of the intrathecal dose of a certain drug, streptomycin, one may assume that the other similar reactions after smaller doses were also due to its intrathecal use. This assumption seemed particularly likely in view of the fact that these were the only such reactions noted in a careful review of the case histories of our last 100 patients with meningitis due to H. influenzae, whether or not intrathecal therapy was given. Although a number of patients showed signs of shock and respiratory irregularity on admission to the hospital, we were surprised to find that the development of such symptoms after the initiation of treatment was observed only in the patients here reported. In each instance when sharp febrile rises occurred, there was a close time relationship to the intrathecal injection. The postmortem findings in Case 6 throw some doubt on the etiology of the clinical picture observed after the second intrathecal injection. However, the similarity to the etiologically better-defined reactions in other patients receiving high intrathecal dosage of streptomycin seemed to justify inclusion of the case. Six of the 25 patients with tuberculous meningitis had similar reactions, which are summarized in the Table. The relation between size of the intrathecal dose and incidence of unfavorable reactions was less striking in this group than in the patients whose meningitis was caused by H. influenzae, since none of the three who received intrathecal injections of 100 mg. showed toxic symptoms. It is worthy of note that both groups of patients tended to be pale, more irritable, and even stuporous on the days when intrathecal therapy was given, and that these signs were related to the size and frequency of the dose. Among the tuberculous patients, those receiving intrathecal therapy often experienced headache and increased malaise and seemed somewhat paler and more inactive on the days when intrathecal injections were given. It was also an almost universal finding in this same group that resumption of intrathecal medication after a rest period resulted in an increase of the cerebrospinal fluid pleocytosis from the existing count of 30 to 100, to 150 to 300, white blood cells. Similar observations of the patients with H. influenzae meningitis could not be made because administration of intrathecal streptomycin was invariably discontinued before the cerebrospinal fluid white cell count had fallen to such low levels. A comparison of daily cerebrospinal fluid white cell levels was also made between the latter patients and 28 children with the same disease who recovered without intrathecal treatment. There was no significant difference between the two groups with respect to rate of fall or duration of pleocytosis.

COMMENT

The foregoing data suggest that there is an appreciable incidence of serious reactions to the intrathecal administration of streptomycin among patients with meningitis, particularly when it is given in large doses at frequent intervals. They also confirm the observations made earlier by Cairns, Duthie and Smith.[1] The pallor, irritability, and stupor noted in a larger number of our patients is consistent with the report of Farrington and his co-workers[6] concerning untoward effects caused by intrathecal streptomycin.

6. Farrington, R. F.; Hull-Smith, H.; Bunn, P. A., and McDermott, W.: Streptomycin Toxicity: Reactions to Highly Purified Drug on Long-Continued Administration to Human Subjects, J. A. M. A. 134: 679 (June 21) 1947.

The nature of the signs and symptoms observed suggests that their etiology lies in a toxic action of streptomycin on medullary centers. The toxicity may be manifested by signs of either depression or irritation. Why this substance should prove toxic in some cases only, and then not with every injection, is a matter for conjecture. Drug impurities are an obvious reason. However, even purified streptomycin has been shown to have adverse side effects when given intrathecally.[6] Untoward reactions occurred in some of our patients in 1948 and 1949 when purified streptomycin (Merck) was used. This tends to rule out impurities as the sole causative factor. Evidence favoring the role of impurities in causing reactions to intrathecal streptomycin is the fact that the reactions in Cases 11 and 12, and in Cases 13 and 14 occurred in each instance in two patients who received intrathecal injections of streptomycin from the same bottle in the same treatment room within half an hour of each other. It is our impression that in 1950 we saw fewer and less severe reactions to intrathecal streptomycin. This accords with the reported[7] continued progress in the manufacture of streptomycin free from impurities. However, we are unable to evaluate this point adequately because of the less frequent use of intrathecal streptomycin in our institution at present plus the fact that smaller doses are employed when it is used. It is reasonable to expect that there may be marked individual variations in susceptibility to the toxic effects of streptomycin on the central nervous system, and this is probably a factor of considerable importance in the production of reactions. We have also noted such variations in individual susceptibility to eighth nerve damage among patients receiving intramuscular streptomycin. There appeared to be a difference in immediate severity of the reactions among the patients with H. influenzae meningitis as compared with those with tuberculous meningitis. This might be explained on the basis of generally greater central nervous system irritability among patients with acute meningitis as opposed to those with a more chronic type. We were unable to make any correlation between the concentration of the solution injected and the occurrence of reactions. The latter occurred when streptomycin was injected in concentrations as low as 2 mg. per cubic centimeter, and did not occur in many instances when concentrations of 10 to 50 mg. per cubic centimeter were used. The highest concentrations used in any of the patients showing reactions was 10 mg. per cubic centimeter, but it was half of that in most cases. The total amount of solution placed in the spinal canal varied between 5 and 20 cc. An equal or slightly greater amount of cerebrospinal fluid was withdrawn immediately before each injection, which usually took place over a period of three to five minutes. The fact that, in certain patients, reactions were observed only after some injections is hard to explain but may be said to depend on variations in the concentration of streptomycin reaching the sites of its toxic action.

In the face of evidence that the intrathecal injection of streptomycin may cause serious toxic reactions other than the well-known eighth-nerve complications, we believe there is a real contraindication to the use of such treatment in any form of meningitis when equally good results can be obtained by some other mode of therapy. The results reported by Hoyne and Brown,[4c] Crook, Clanton, and Hodes,[3b] and McKay, Davies and Winter[5] provide excellent evidence that meningitis due to H. influenzae is such an instance especially since aureomycin and chloramphenicol have been added to the list of therapeutic agents effective against that organism. Levinson's[8] paper suggests that the same may be true in the case of tuberculous meningitis, but the evidence for this is less conclusive. It seems probable that, in a similar way, the use of intrathecal streptomycin will be found to offer hazards without advantage in other forms of meningitis as well.

SUMMARY

The occurrence of 14 serious reactions with three probable and two possible fatalities among 90 patients treated for meningitis with repeated injections of intrathecal streptomycin is reported. Eight cases are described in detail. The reactions consisted chiefly of shock-like states with slow, irregular respirations, inability to handle adequately the secretions of the upper respiratory tract, convulsions, cerebellar signs, and marked rises in body temperature, with peak severity usually appearing five to six hours after the intrathecal injection. The symptoms were not identical in each instance and occasionally occurred immediately after withdrawal of the lumbar puncture needle. There appeared to be some relationship between the size of the intrathecal dose and the occurrence of reaction.

Clinical impression of an even higher incidence of mild reactions, consisting of pallor, irritability, loss of appetite, and stupor, is mentioned.

When equally good results can be obtained without it, discontinuance of the intrathecal use of streptomycin is advocated on the basis that it is uncomfortable to the patient, unnecessary, and dangerous.

University of Vermont College of Medicine, Burlington, Vt. (Dr. McKay).

7. Merck & Co., Personal communication to the author.

8. Levinson, A.: Streptomycin Therapy in Tuberculous Meningitis, Am. J. Dis. Child. 77: 709 (June) 1949.

Advice to Young Physicians.—You start your lives with the fresh outlook and the generous ideals of youth, but you start it with the handicap which youth places on the young physician. You are uncertain of human reactions, and about that what can I say to you? Is it not something very simple—to be simple yourselves, to observe without being observed, to listen to what is said to you, for it is often an outlet for pent-up emotions and fear, and a sympathetic hearing gives comfort and leads to mutual understanding. Avoid pomposity of word or manner, and eschew familiarity. Give that examination which is the patient's due and without which no decision can be made. Refrain from speaking in stereotyped paraphrase or periphrasis which too often means nothing but the evasion of a difficult duty. Those who seek your help are ignorant of medicine but are oftener than not intelligent. They are anxious in mind and have asked for your decision. Tell them what you think in simple but precise terms, and if you cannot reach a decision be equally honest. They will appreciate your difficulties and think the more of you for that confession. The patient can cooperate with the physician only if confidence is complete.—Charles Cameron, M.D., The Physician and His Art, *Lancet*, Aug. 25, 1951.

RESPONSE OF PLASMODIUM MALARIAE INFECTIONS TO THREE DIFFERENT DRUGS

RESPONSE TO METACHLORIDINE, CHLOROGUANIDE ("PALUDRINE"), AND INTRAMUSCULAR CHLOROQUINE

Sol B. McLendon, M.D.
and
Martin D. Young, Sc.D., Columbia, S. C.

In the search for more efficient drugs in the treatment of Plasmodium malariae, the causative agent of quartan malaria, tests were made with metachloridine, chloroguanide hydrochloride and intramuscular chloroquine.

Metachloridine, a sulfonamide with the formula N¹-(5-chloro-2-pyrimidyl) metanilamide, was found in a field study by Kenney and Brackett [1] (1947) to suppress natural infections of P. malariae.

At the time the work reported here was started, the few scattered reports (Fairley,[2] Afridi,[3] Jafar,[4] Parekh and Boghani,[5] and Viswanathan and Baily [6]) on the treatment of P. malariae with chloroguanide gave results ranging from satisfactory to unsatisfactory or inconclusive, the latter owing to the small number of cases or lack of adequate data.

The action of chloroquine diphosphate given orally against our strain of P. malariae infections has been reported previously.[7] Later, Culwell and others [8] (1948) and Spicknall and others [9] (1949) found that chloroquine administered intramuscularly and followed by oral dosages gave good results against plasmodium vivax and plasmodium falciparum infections.

The present report presents the results of therapeutic trials of these drugs against the United States Public Health Service strain of P. malariae.

METHODS

Except for one patient, the malaria infections were induced in neurosyphilitic patients by the intravenous injection of blood containing from 1,000,000 to 135,000,000 parasites. One patient received sporozoites injected intravenously. Blood smears were made daily. Parasite densities were determined by counting the parasites in at least 0.1 cu. mm. of blood. Fevers were defined as oral temperatures of 100 F. or over. The dosages of drugs used were as follows: metachloridine,[10] 0.5 gm. orally every six hours for six days; chloroguanide, 0.1

Parasitologic and Clinical Response of P. Malariae Infections to Different Drugs

Patient	Number of Fevers Before Start of Therapy	Parasites per Cubic Millimeter On First Day of Therapy	Parasites Removed in 24 Hours, %	Days Until Negative Smear	Days Until Afebrile (< 100 F.)
Metachloridine 0.5 Gm. Every 6 Hours for 6 Days					
J. H. T.	20	5,440	0	14	6
R. S.	18	3,376	29	10	2
C. C.	33	8,050	40	18	5
J. W.	25	1,562	*	7	0
A. L.	24	4,228	18	12	4
W. C.	25	5,750	47	9	5
F. J.	31	3,850	*	14	5
W. M.	26	1,287	†	8	2
J. H. J.	21	3,102	80	12	2
P. G.	20	2,332	28	15	6
Chloroguanide 0.1 Gm. Three Times Daily For 10 Days					
A. H.	28	4,290	58	6	0
O. S.	15	7,160	*	13	5
F. Q.	31	2,090	†	13	0
C. L.	35	1,520	6	10	0
E. B.	21	1,552	33	14	0
J. H. R.	28	2,440	*	8	1
E. R.	24	908	36	12	0
Chloroquine Dihydrochloride, Single Intramuscular Injection of 225 Mg.					
O. S.	9	17,550	†	11 ‡	2 §
G. D.	16	6,420	58	§	2 §
W. N.	23	3,733	54	¶	3 §
N. L.	15	16,512	37	‡	4 §
Chloroquine Dihydrochloride, Single Intramuscular Injection 450 Mg.					
N. L.	18	29,825	79	10	2
G. D.	23	9,840	84	4	2
W. N.	28	4,833	94	3	0
C. W.	8	18,308	65	5	0
A. P.	7	2,140	80	7	2
J. T. W.	7	9,150	11	10	0
C. G.	14	4,080	65	4	0
A. G.	5	3,630	87	5	2
S. W. P.	2	6,350	79	5	2
R. M.	21	2,820	95	5	0
E. C.	1	7,080	57	7	2
M. T. C.**	13	5,150	98	2	1

* Parasites increased.
† No data on this day.
‡ Relapsed 18 days later.
§ Fevers returned later.
‖ Still positive after 28 days.
¶ Still positive after 18 days.
‡ Still positive after 16 days.
** Sporozoite-induced. All others induced by injection of infected blood.

From the South Carolina State Hospital (Dr. McLendon), and the Federal Security Agency, Public Health Service, National Institutes of Health, Microbiological Institute, Laboratory of Tropical Diseases (Dr. Young).

1. Kenney, M., and Brackett, S.: The Effectiveness of Metachloridine in Suppressing Natural Infections with Plasmodium malariae and P. Falciparum in British Guiana, Am. J. Trop. Med. **27**: 493-501, 1947.
2. Fairley, N. H.: Researches on Paludrine (M4888) in Malaria: Experimental Investigation Undertaken by L. H. Q. Medical Research Unit (A. I. F.), Cairns, Australia, Tr. Roy. Soc. Trop. Med. & Hyg. **40**: 105-162, 1946.
3. Afridi, M. K.: A Critical Review of Therapeutic Trials on Paludrine Carried out in India During 1946, Ind. J. Malaria **1**: 347-359, 1947.
4. Jafar, M.: Preliminary Report on the Use of Paludrine in the Field, Ind. J. Malaria **1**: 365-368, 1947.
5. Parekh, J. G., and Boghani, B. P.: Report on the Use of Paludrine Tablets, Ind. J. Malaria **1**: 383-387, 1947.
6. Viswanathan, D. K., and Baily, J. D.: Experiments with Paludrine in the Chemotherapy of Malaria, Ind. J. Malaria, **1**: 307-328, 1947.
7. Young, M. D., and Eyles, D. E.: The Efficacy of Chloroquine, Quinacrine, Quinine, and Totaquine in the Treatment of *Plasmodium Malariae* Infections (Quartan Malaria), Am. J. Trop. Med. **28**: 23-28, 1948.
8. Culwell, W. B.; Cooper, W. C.; White, W. C.; Lints, H. A., and Coatney, G. R.: Studies in Human Malaria: XX. The Intramuscular Administration of Chloroquine, J. Nat. Malaria Soc. **7**: 311-315, 1948.
9. Spicknall, C. G.; Terry, L. L., and Coatney, G. R.: The Treatment of Falciparum Malaria with Intramuscular Chloroquine, Am. J. M. Sc. **218**: 374-377, 1949.
10. The metachloridine—N¹-(5-chloro-2-pyrimidyl) metanilamide—was supplied by the American Cyanamid Company, Stamford Conn., the chloroguanide by the DuPont Company, Wilmington, Del., and the chloroquine, in sealed ampules of 5 cc each, by Winthrop-Stearns, Inc., New York.

gm. orally three times daily for 10 days; chloroquine dihydrochloride, a single intramuscular injection of 225 mg. in 5 cc. of solution; chloroquine dihydrochloride, a single intramuscular injection of 450 mg. in 10 cc. of solution.

The injections were made into the gluteal muscles. The chloroquine dihydrochloride salt is equivalent to 89% of the base.

RESULTS

No toxic reactions to any of the drugs were observed. After the injection of chloroquine, even in 10-cc. amounts, there were no changes at the site of injection, or discomfort experienced by the patient.

The response of the infections to the drugs is shown in the table. A patient receiving metachloridine first had a negative blood test seven days after the beginning of treatment; the median for disappearance of parasites for the 10 patients was 12 days (mean, 11.9 days). Even though the treatment was begun late in the primary attack, the elimination of clinical symptoms also was slow. With chloroguanide therapy, the first negative blood was on the sixth day after the beginning of treatment, and the median for clearance of parasites from the blood stream was 12 days (mean, 10.9). One patient had five fever paroxysms and another had one fever after institution of treatment. The other five patients had no fevers after treatment, but this may have been due in part to the length of the primary attack before treatment.

Chloroquine dihydrochloride, 225 mg., given intramuscularly, elicited an unsatisfactory response. One patient became negative for blood parasites on the 11th day, but parasites reappeared 18 days later. The other three patients had only a temporary diminution in the number of parasites for about one week, after which the number returned to the pretreatment range. The fevers followed the pattern of the parasites, abating only temporarily.

A single intramuscular injection of 445 mg. of chloroquine dihydrochloride gave the fastest clearance of the parasites from the blood stream (first negative blood, two days; median, five days; mean, 5.6 days). The fevers also abated rapidly. Five of the patients had no fevers after treatment and the other seven had only one fever each.

COMMENT

The report of Kenney and Brackett [1] that metachloridine completely suppressed natural infections of P. malariae gave hope that this parasite might be highly sensitive to the drug. However, the results of the present work indicate that therapeutically metachloridine is not as active as chloroquine.

Chloroguanide, although perhaps slightly superior to metachloridine, was not so effective as 1.5 gm. of chloroquine administered orally (Young and Eyles [7]).

After we began this work, Ciuca and others [11] (1948) reported on the use of chloroguanide in treatment of 25 patients with blood-induced P. malariae. Their results also showed that infections caused by this parasite had a fairly high degree of resistance to chloroguanide.

The single injection of 225 mg. of chloroquine was not an effective therapeutic dose. Because it caused a temporary diminution of parasites and abatement of fevers, which later returned to normal ranges, this dose might be useful in neurosyphilitic patients undergoing a course of quartan malaria, if and when it is desirable to give the patient a respite from the infection without eliminating it altogether.

The single intramuscular injection of 450 mg. of chloroquine dihydrochloride gave results comparable with oral doses of the same drug totaling 1.5 gm. and 2.4 gm. previously reported by Young and Eyles,[7] using the same strain of malaria. The removal of the parasites from the blood stream and the elimination of the fevers were relatively rapid.

The obvious advantage of treating P. malariae infections with a single injection of the drug should make chloroquine the method of choice in many cases involving this parasite.

SUMMARY AND CONCLUSIONS

1. The efficacy of metachloridine—N[1]-(5-chloro-2-pyrimidyl) metanilamide, chloroguanide ("paludrine") and the intramuscular chloroquine dihydrochloride was tested in 33 induced infections of Plasmodium malariae.

2. No toxic reactions from any of the drugs were noticed.

3. The poorest results were obtained with metachloridine. Chloroguanide gave only slightly better results, but was not so effective as oral or intramuscular chloroquine.

4. Chloroquine dihydrochloride given in a single intramuscular injection of 450 mg. produced the best results. The removal of parasites from the blood stream and the elimination of fevers were relatively rapid. The action was very similar to that obtained by oral administration of chloroquine in doses totaling 1.5 and 2.4 gm. The intramuscular method has the obvious advantage of requiring only one injection.

Federal Security Agency, Public Health Service, P. O. Box 717 (Dr. Young).

11. Ciuca, M.; Soflete, A.; Constantinesco, P., and Teriteanu, N.: Preliminary Note on the Therapy of Malaria with Paludrine in Experimental Infection by Inoculation of Infected Blood, Bull. World Health Organ. 1: 301-307, 1948.

Understanding the Patient.—You cannot help a man if you dislike him, and the only alternative to dislike is to work at understanding. You may feel that you are beyond prejudices, and perhaps some of you are, but I suggest that you examine your attitude towards the sick young man who is very dependent on his mother, toward people who whine and beg for relief from pain, toward the woman who does not want to have any more children, toward patients unwilling to leave the hospital, relatives who won't sign permission for post mortem examination, overanxious mothers who call all the time about their children, relatives who know a little medicine and try to tell you how to treat the patient, toward patients who always get an acute pain at 3 a. m., and patients with vague undiagnosible aches and pains who keep coming back in spite of your having told them they are not ill. If you find yourselves turning away from these people, feeling put upon by them, labeling them "crocks," "bores," and "nuisances," then you need to discipline yourselves if you are going to have any success in the full practice of medicine. They are sick, they need an understanding doctor, they deserve courtesy, understanding and help.—Isidor S. Ravdin, M.D., The Art of Medicine, *New York Medicine*, Aug. 5, 1951.

TREATMENT OF MULTIPLE MYELOMA WITH URETHAN

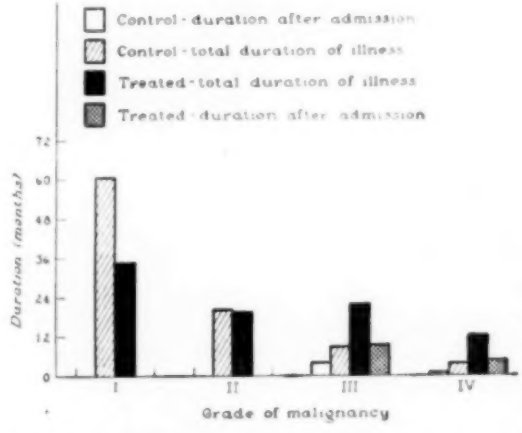
EXPERIENCE WITH SIXTY-SIX CASES OVER A TWO-AND-A-HALF-YEAR PERIOD

William F. Luttgens, M.D.
and
Edwin D. Bayrd, M.D., Rochester, Minn.

Since 1946 a number of reports have appeared on the use of urethan (ethyl carbamate) in the treatment of various malignant diseases, including multiple myeloma. The results from treatment of the first few patients with multiple myeloma were not encouraging.[1] In 1947, however, Alwall [2] reported his findings in two patients, one of whom experienced almost complete recovery, both objectively and subjectively, upon prolonged treatment with urethan. The hemoglobin content, erythrocyte count, erythrocyte sedimentation rate, total serum proteins, and albumin-globulin ratio returned to normal; albuminuria disappeared; plasma myeloma cells disappeared from the sternal marrow, and only unchanged roentgenograms remained as evidence of the original process. Subsequent reports by Loge and Rundles,[3] Harrington and Moloney,[4] and others [5] have been encouraging, but none matched the dramatic result recorded by Alwall.

METHOD OF STUDY

From January, 1948, through June, 1950, urethan was administered to 66 patients, about two-thirds of the patients with myeloma registering at the Mayo Clinic during that period. At first the drug was given as a liquid solution containing 0.5 gm. per teaspoonful, to be taken by mouth after meals diluted with a glass of water. Later, tablets containing 5 grains (0.3 gm.) of urethan became available. In at least one patient, difficulty was encountered from almost intact tablets appearing in the stool. The dosage objective was, in general, the maximal amount tolerated by the patient. Starting initially with 1.5 to 3.0 gm. in divided doses three times daily after meals, the daily dose was increased gradually by approximately 0.5 gm. increments every few days until the maximal amount tolerated had been reached. Eleven patients received urethan by intravenous injection in a daily dose of 4 gm. in 1,000 cc. of 5% solution of dextrose in water. Four of these patients received intravenous urethan alone in amounts ranging from 24 to 68 gm. Seven patients received 40 to 100 gm. of urethan intravenously, in addition to oral medication. Thirteen of the 55 patients receiving urethan orally only, apparently unable to tolerate even small amounts, took less than 100 gm. These patients will not be considered further here, since such treatment was deemed to be inadequate. Including the seven patients who received combined therapy, 49 patients were given 100 gm. or more of urethan with the exception of five patients who died while under treatment and received a total of only 37 to 77 gm. It would have been statistically improper to exclude these patients; hence, they are retained despite inadequate treatment. The average amount of urethan administered was 420 gm. over a period of 11.7 mo. Satisfactory bone marrow smears, usually from the sternum, were obtained from all but one patient. Values for hemoglobin concentration, erythrocyte, leukocyte, differential and platelet counts, erythrocyte sedimentation rate (Westergren method), Bence Jones proteinuria, total serum protein, albumin-globulin ratio, and blood urea were routinely obtained, as were roentgenograms of the thorax, skull, and spinal column. Patients were instructed to have interim blood counts done under the direction of their home physician.



Comparison of survivals of urethan-treated and control groups of patients having multiple myeloma.

The degree of malignancy of the myeloma plasma cells obtained by bone marrow aspiration and stained with Wright's stain was estimated in all cases in accordance with criteria set forth previously.[6a] Grading of malignancy was on a basis of I to IV, in which I represents the least and IV the most malignant condition. Enumeration of myeloma plasma cells per 200 leukocytes in unconcentrated marrow smears was performed in 20 cases in which repeated examinations were possible.

RESULTS

Duration of Life.—A comparison of the 48 urethan-treated patients, on whom satisfactory marrow smears were obtained, with the patients in a control group reported earlier, is presented in Table 1 and the Figure.[6] Both groups include patients treated at the clinic and elsewhere with ionizing radiation or stilbamidine (4,4'-diamidinostilbene) or both. All of the previously treated patients in the control group are dead, while only approximately a third of the urethan-treated patients had died at the time these data were obtained. Because the great variability in duration of illness correlates fairly well with the cell type present,[6a] both groups are compared according to the estimated degree of malignancy

Fellow in Medicine, Mayo Foundation (Dr. Luttgens); from the Division of Medicine, Mayo Clinic (Dr. Bayrd).

1. Paterson, E.; Haddow, A.; Thomas, I. A., and Watkinson, J. M.: Leukaemia Treated with Urethane Compared with Deep X-ray Therapy, Lancet **1**: 677-682 (May 11) 1946. Berman, L., and Axelrod, A. R.: The Effect of Urethane on Malignant Diseases: Clinical, Hematologic and Histologic Observations on Patients with Carcinoma, Leukemia and Related Diseases, Am. J. Clin. Path. **18**: 104-129 (Feb.) 1948. Wilson, S. J.; Wise, G. W., Jr., and Campbell, J. W.: The Treatment of Leukemia and Allied Disorders with Urethane (Ethyl Carbamate), J. Kansas M. Soc. **49**: 97-100 (March) 1948.

2. Alwall, N.: Urethane and Stilbamidine in Multiple Myeloma: A Report on 2 Cases, Lancet **2**: 388-389 (Sept. 13) 1947.

3. Loge, J. P., and Rundles, R. W.: Urethane (Ethyl Carbamate) Therapy in Multiple Myeloma, Blood **4**: 201-216 (March) 1949.

4. Harrington, W. J., and Moloney, W. C.: The Treatment of Multiple Myeloma with Urethane, Cancer **3**: 253-271 (March) 1950.

5. Saltzman, F., and Borgström, H.: Multiple Plasmacytoma Treated with Urethane: A Case Report, Acta med. Scandinav. **136**: 388-392, 1950. Derifield, R. S.: The Effect of Urethane in Multiple Myeloma: A Report of 4 Cases, J. Iowa M. Soc. **40**: 220-223 (May) 1950.

6. (*a*) Bayrd, E. D.: The Bone Marrow on Sternal Aspiration in Multiple Myeloma, Blood **3**: 987-1018 (Sept.) 1948. (*b*) Bayrd, E. D., and Heck, F. J.: Multiple Myeloma: A Review of 83 Proved Cases, J. A. M. A. **133**: 147-157 (Jan. 18) 1947.

of the disease. For the groups graded III and IV, the total duration of illness of the urethan-treated group at the time these data were obtained already exceeded that of the control group, despite the fact that most of the treated patients were still living. This was true whether survival was calculated from the time of admission or from the onset of symptoms. Although the groups are small, the evidence suggests that life is prolonged by the use of urethan. The duration of illness for group II patients treated with urethan was, at the time these data were obtained, about the same as that for the control group, although a majority of the former group were still alive. Insufficient time has passed to permit any conclusions about the group I patients, whose duration of illness, without urethan treatment, was up to 101 mo. in the control group.

Improvement.—The degree of objective and subjective change was determined in each of the 48 patients when possible. A few patients were not examined at the clinic after treatment; therefore, the number of adequate observations of objective change was less than that of subjective change. Improvement was graded on a basis of 0 to 4. Zero means that the patients became worse (natural course of the disease was unaltered); 1 indicates no change or slight improvement; 2, moderate improvement; 3, marked improvement, and 4, apparent complete return to normal. The maximal improvement at any time was recorded. These findings are shown in Table 2.

Subjective Improvement: About half of the patients had definite relief of symptoms following treatment, but only two were completely relieved. This improvement was seen particularly in those having a milder form of the disease. Conversely, progression despite therapy was seen especially in those with a very malignant bone-marrow picture.

Objective Improvement: Objective improvement was encountered less frequently than subjective improvement. No patient had a complete objective remission, and only one was considered to show marked improvement. Here again, improvement was seen most often in those patients having the less malignant disease. Others were but slightly improved or became worse. Some of the objective changes will be considered separately in succeeding paragraphs.

Hemoglobin: Forty patients had repeated hemoglobin determinations, in 90% of which the concentration was initially less than 12.5 gm. per 100 cc. Thirteen showed an improvement in hemoglobin concentration, the increases ranging from 1 to 3 gm. per 100 cc. This was one of the most frequent objective signs of improvement.

Erythrocyte Sedimentation Rate: There were 20 patients who in repeated determinations had sedimentation rates (Westergren) exceeding 100 mm. in one hour. In seven of these the sedimentation rate fell 20 to 30 mm. with treatment. In two instances improvement was greater but not to within the normal range. Of seven patients whose sedimentation rates were in the range of 50 to 100 mm. per hour, on repeated examinations 2 of these patients' sedimentation rates fell to the normal range, although these falls occurred several months after treatment was discontinued. Three patients had sedimentation rates of less than 35 mm. per hour, which returned to normal or near normal levels with therapy. The sedimentation rates of the remaining patients were unimproved, or the patients had only single determinations. Decrease in sedimentation rate was the most frequent objective manifestation of improvement.

Serum Proteins: Of 20 patients with abnormalities of their serum proteins who had repeated determinations, definite improvement was noted in only one. In five others there was equivocal improvement. Improvement, when noted, consisted of a decrease in serum globulin and total serum proteins, with or without an increase in serum albumin. In none of these patients were the serum proteins observed to return to normal.

TABLE 1.—*Data on Patients Who Had Multiple Myeloma*

	Control Group				Urethan-Treated Group			
Estimated Degree of Malignancy	Patients	Patients Dead	Average Duration of Illness, Mo.	Average Duration Since Admission, Mo.	Patients	Patients Dead	Average Duration of Illness, Mo.*	Average Duration Since Admission, Mo.
I	7	7	61	..	8	6	34.6	...
II	24	24	22.3	..	22	10	22	...
III	5	5	9	4	12	3	21.9	10.6
IV	5	5	3.6	1	6	2	12.5	4.6
Total	41	41	25†	..	48	15	22.8†	...

* All patients, living and dead.
† Average.

TABLE 2.—*Amount of Improvement*

Degree of Improvement		Estimated Degree of Malignancy I	II	III	IV	Total
Objective						
0	Patients	1	5	5	2	13
	Per cent	12.5	29	50	67	31
1	Patients	6	6	4	1	17
	Per cent	75	36	40	33	45
2	Patients	1	5	1	0	7
	Per cent	12.5	29	10	0	18
3	Patients	0	1	0	0	1
	Per cent	0	6	0	0	3
4	Patients	0	0	0	0	0
	Per cent	0	0	0	0	0
Subjective						
0	Patients	0	8	3	4	15
	Per cent	0	36	25	67	31
1	Patients	4	4	3	0	11
	Per cent	50	18	25	0	23
2	Patients	2	7	3	2	14
	Per cent	25	32	25	33	29
3	Patients	1	2	3	0	6
	Per cent	12.5	9	25	0	13
4	Patients	1	1	0	0	2
	Per cent	12.5	5	0	0	4

Bence Jones Protein: Thirteen patients with Bence Jones proteinuria had repeated urine examinations; in none did the protein disappear during or after treatment.

Blood Urea: Six of the 48 patients had blood urea values initially of more than 50 mg. per 100 cc. In two of these, with repeated determinations, the blood urea was essentially unchanged after therapy, although no more than 50 gm. of urethan was administered in each case. Both patients were dead within two months. In one of these two patients the blood urea rose from 72 mg. per 100 cc. to 142 mg. and fell again to 60 mg. when treatment was discontinued. A similar pattern was seen in the other patient given urethan intravenously. All but one of the four remaining patients with blood urea values ranging from 54 to 68 mg. per 100 cc. were dead within nine months. The exception was the only patient in this

group of 6 patients with myeloma of a low estimated degree of malignancy.

Roentgenograms: Twenty-six patients had repeated roentgenographic examinations. Improvement of an equivocal nature only was seen in three after therapy.

Bone Marrow: Bone marrow aspiration was repeated during and after therapy in 20 cases. The percentage of myeloma plasma cells was essentially unchanged in eight, increased in five, and decreased in seven. The decreases were seen most frequently immediately after a course of intravenous therapy. These changes did not appear to be related to the degree of malignancy or to the amount of improvement otherwise shown by the patient after treatment. No change in the degree of malignancy was noted.

TOXIC EFFECTS OF URETHAN

Leukopenia.—A fall in the number of leukocytes to less than 4,000 per cubic millimeter of blood at some time during therapy was seen in about 75% of those in whom repeated determinations were done. In about 25% the leukocyte count fell to 2,000 per cubic millimeter or less. The polymorphonuclear neutrophil and lymphocyte count were generally symmetrically depressed, although a disproportionately greater fall in the lymphocyte count was not infrequent. No complications attributable to the leukopenia were encountered. In only five instances was it deemed necessary to interrupt therapy on this account. Generally, the leukocyte count rose as treatment was continued. Leukopenia was seen in almost all patients receiving urethan intravenously, but permanent discontinuance of the drug for this reason was never necessary. Leukopenia did not seem to be a requisite for a favorable response to treatment.

TABLE 3.—*Laboratory Data for Patient with Multiple Myeloma*

	Feb., 1950	Sept., 1950
Hemoglobin (gm. per 100 cc.)	12.7	14.1
Sedimentation rate (mm. per hr., Westergren)	100	55
Total serum proteins (gm. per 100 cc.)	10.1	9.9
Albumin	3.2	3.3
Globulin	6.9	6.6
Proteinuria	None	None
Myeloma plasma cells in sternal bone marrow (%)	50	7

Thrombopenia or pancytopenia was not encountered as a result of therapy, despite a total in excess of 1,600 gm. of urethan administered to one patient in a single course of urethan therapy. The hemoglobin concentration and erythrocyte count frequently improved after therapy, and any fall in the values for the hemoglobin concentration and erythrocyte count appeared more likely to be the result of the disease process itself than a toxic effect of the medication.

Gastrointestinal Symptoms.—Anorexia, nausea, vomiting, or diarrhea was noted in at least two-thirds of the patients. Of the 13 patients who were not included in the study because they had taken less than 100 gm., 11 were forced to discontinue the drug permanently because of symptoms of gastrointestinal irritation. Among the 49 patients who took at least 100 gm. of urethan, gastrointestinal irritation forced reduction of daily dosage to as low as 0.5 gm. per day or alternation of weeks on medication. Only a rare individual seemed to be able to take 2 or 3 gm. daily, regularly, without difficulty, and a dose of 4 or 5 gm. daily was seldom possible, even when treatment was given on alternate weeks. Attempts to overcome this difficulty by having the patient dilute the drug well with water and take it immediately after meals (as all did) or take the drug in tablet form met with only partial success.

INTRAVENOUS MEDICATION

Urethan[7] seemed to be better tolerated when used intravenously than orally, although some patients became nauseated even after intravenous administration. Twenty-four to 92 gm. was given in a relatively short period, generally two weeks, in daily doses of 4 gm. in 1,000 cc. of 5% solution of dextrose in water. Eleven patients received intravenous therapy, four receiving intravenous therapy only and seven receiving both oral and intravenous therapy. Patients receiving intravenous therapy were among those in most acute distress, frequently being unable to turn in bed. Subjective improvement appeared to be prompter and more striking than that noted with only the oral use of urethan, although the number of patients responding seemed no greater. Leukopenia was seen more commonly in this group, necessitating frequent leukocyte and differential counts, and therapy was interrupted occasionally although no complications were encountered. Decrease in the percentage of plasma myeloma cells in the bone marrow, when seen, occurred most frequently after a course of intravenous therapy. In one patient with a blood urea of 62 mg. per 100 cc., there was an increase to 150 mg. per 100 cc. while under intravenous treatment.

The following case report is about a patient, one of those most improved, who received combined therapy.

REPORT OF A CASE

A Spanish-American merchant, 53, was admitted to the hospital with severe back pain. His illness had begun three months earlier with stiffness of the neck and thoracic pain. Swellings had appeared over his sternum and ribs, one of which was fractured after slight trauma. A month before admission he had begun to have spasms of severe girdle pain in the thoracic and lumbar regions, precipitated by coughing or motion of the trunk. The pain had become progressively incapacitating.

On physical examination a tumor (8 cm. in diameter) involving the upper part of the sternum was found. The patient was unable to turn because of pain, and merely moving the bed would precipitate a "spasm" of pain.

Roentgenographic examination of the thorax, skull, spinal column, and pelvis revealed marked osteoporosis with regions of destruction of bone. There was compression of the ninth and 12th thoracic and fifth lumbar vertebrae. Sternal-marrow smears revealed a large number of myeloma plasma cells of intermediate malignancy (grade II). Additional laboratory data are listed in Table 3.

Intravenous administration of 4 gm. of urethan daily in 1,000 cc. of 5% solution of dextrose in water was begun. The patient's leukocyte count fell to 2,200 per cubic millimeter, but treatment was not interrupted. Eighteen days later, after receiving 72 gm. of urethan, he felt "50% better" and walked for an hour and a half, for the first time in one-and-a-half months. A month after treatment was started, he was dismissed, still having some thoracic pain.

Six months later the patient returned, having taken 525 gm. of urethan orally, an average of about 3 gm. daily. Despite a better-than-average tolerance for the drug, anorexia became a disagreeable problem. He was able to drive his automobile,

7. Supplied in part by Eli Lilly and Company.

attend his business, and go swimming. He had pain occasionally in his neck and shoulders but was "85 to 90% better." The sternal mass had decreased in size by half.

Roentgenographic examination revealed the rib lesions generally to be smaller, the skull the same, and the spinal column and pelvis worse. Other laboratory data, before and after treatment, are listed in Table 3.

SUMMARY AND CONCLUSIONS

Sixty-six patients with pathologically proved multiple myeloma were treated with urethan (ethyl carbamate) over a two-and-a-half-year period. Of these, 13 patients, unable to tolerate the drug, discontinued treatment before receiving an adequate amount (less than 100 gm.). Four received urethan intravenously only, and seven received it both intravenously and orally. Forty-eight patients, including the foregoing seven, given adequate therapy or succumbing while under treatment were studied for survival time and subjective and objective improvement. The degree of malignancy of the disease was estimated, and on that basis the cases were compared with those of a control group similarly studied in which the patients had obtained the customary treatment previously available. There was some suggestion that life was prolonged in the urethan-treated group.

About half of those treated with urethan felt definitely better, but only about a fifth appeared to be objectively improved. Objective improvement was never marked and was noted usually in those with a less malignant grade of the disease.

Increase in hemoglobin concentration and decrease in erythrocyte sedimentation rate were the most frequently encountered signs of improvement. There was no great change in serum proteins, roentgenographic findings, or the percentage of myeloma cells in the bone marrow. Bence Jones proteinuria did not disappear with treatment. Leukopenia occurred in three-fourths of the patients, but no complication attributable to this occurred. Gastrointestinal symptoms were noted in two-thirds of the patients; rarely was any patient able to take regularly the desired daily dose of at least 3 gm. There was no essential difference in the response of the small group given intravenous therapy, except for fewer gastrointestinal symptoms and prompter subjective improvement. While the results recorded are not too encouraging, administration of urethan is probably as good treatment as is available for multiple myeloma at the present time.

102 Second Ave. S. W. (Dr. Bayrd).

ACQUIRED HEMOLYTIC ANEMIA TREATED WITH CORTICOTROPIN

William R. Best, M.D., Louis R. Limarzi, M.D.
and
Henry G. Poncher, M.D., Chicago

Idiopathic, acquired hemolytic anemia is an interesting and perplexing hematological syndrome. Until recent reports of remission following administration of pituitary corticotropin (ACTH), treatment has been unsatisfactory in a large percentage of cases. Use of corticotropin in this disorder was first reported by several investigators at the Blood Club meeting in Atlantic City during April, 1950. These informal presentations were later abstracted [1] and other cases have been cited.[2] A rapid change of the blood picture toward normal has been uniformly noted. Some cases have remained in remission for weeks to months, while others have required maintenance doses to prevent relapse. Whereas most studies of corticotropin effect on normals have failed to show significant alteration of circulating antibodies,[3] some of these hemolytic anemia cases exhibited falling titers in the developing (Coombs) [4] test and other hemagglutinins under therapy. In those cases so tested osmotic and mechanical fragilities returned to normal.

Recently we have observed two cases of acquired hemolytic anemia in the wards of the Illinois Research and Educational Hospitals, Chicago.

REPORT OF CASES

CASE 1.—A white woman, 19, was originally admitted to the Medical Service in June 1947.[5] Shortly after the onset of an upper respiratory infection severe anemia with jaundice developed. Hepatomegaly, splenomegaly, jaundice, pallor, fever of 101 F., and tachycardia of 120 per minute were present on admission. Acquired hemolytic anemia with macrocytosis was diagnosed on the basis of these and the laboratory findings (upper half of table). The Coombs test was strongly positive,[6] and it was difficult to cross match her blood (type A, Rh-positive) with any other. Splenectomy was performed on the third hospital day. The spleen weighed 300 gm., and histological sections were compatible with the diagnosis of hemolytic anemia and hemosiderosis. Hemolysis continued unabated postoperatively, and the temperature remained elevated to 99 to 102 F.

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From the Departments of Internal Medicine and Pediatrics, University of Illinois College of Medicine.

1. (*a*) Gardner, F.: In Discussion on ACTH in Leukemia, News and Views, Blood **5**: 791 (Aug.) 1950. (*b*) Dameshek, W.: In Discussion on ACTH in Leukemia, News and Views, Blood **5**: 791 (Aug.) 1950. (*c*) Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R. Jr.; Roche, M.; Staehelin, D., and Wilson, D. L.: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**: 824 (May 25) 1950.

2. Dameshek, W.; Rosenthal, M. C., and Schwartz, L. I.: The Treatment of Acquired Hemolytic Anemia with Adrenocorticotrophic Hormone (ACTH), New England J. Med. **244**: 117 (Jan. 25) 1951. Gardner, F. H.; McElfresh, A. E.; Harris, J. W., and Diamond, L. K.: The Effect of Adrenocorticotrophic Hormone (ACTH) in Idiopathic Acquired Hemolytic Anemia as Related to the Hemolytic Mechanisms, J. Lab. & Clin. Med. **37**: 444 (March) 1951. Young, L. E.; Christian, R. M., and Izzo, M. J.: Some Newer Concepts of "Congenital" and "Acquired" Hemolytic Anemias, M. Clin. North America **35**: 571 (March) 1951. Unger, L. J.: The Effect of ACTH in Acquired Hemolytic Anemia, Am. J. Clin. Path. **21**: 456 (May) 1951.

3. Thorn, G.: Hematologic Effects of ACTH and Cortisone, in Discussion on ACTH in Leukemia, News and Views, Blood **5**: 785 (Aug.) 1950.

4. Singer, K., and Motulsky, A. G.: The Developing (Coombs) Test in Spherocytic Hemolytic Anemias: Its Significance for Pathophysiology of Spherocytosis and Splenic Hemolysis, J. Lab. & Clin. Med. **34**: 768 (June) 1949.

5. The first admission of this patient was briefly reported as case 5 by Cole, W. H.; Walter, L., and Limarzi, L. R.: Indications and Results of Splenectomy, Ann. Surg. **129**: 702 (May) 1949.

6. Dr. Israel Davidsohn performed most of the serologic tests in these two cases.

despite penicillin therapy. Bacteriologic studies revealed no abnormalities. Two months postoperatively the patient was given 1.0 gm. of streptomycin daily for three weeks. The temperature became normal within six days, and remission of the hemolytic anemia was prompt. The hematocrit determination increased from 13 to 36% in two weeks, and the patient was later discharged in complete remission. During the four months of hospitalization, she received over 80 pt. (40,000 cc.) of whole blood and resuspended cells of types A, Rh-positive; A, Rh-negative, and O, Rh-negative.

The patient was hospitalized for observation one year later and found to be clinically well, with only mild anemia (center of table). Six months later she delivered a normal infant elsewhere without exacerbation of the hemolytic process.

She remained in good health until one week prior to the present admission on Aug. 5, 1950. The current episode began with severe, unrelenting headaches followed in two days by jaundice and vomiting. She noted tenderness in her right upper quadrant and stated that her urine was red. Physical examination revealed hepatomegaly, anemia, jaundice, temperature of 100.6 F., and pulse rate of 100. Laboratory studies showed an acute exacerbation of the hemolytic anemia, with marked leukocytosis, anemia, increase of serum bilirubin, and a normoblastic reaction of the bone marrow (lower part of table). Because the patient was critically ill, the period of observation prior to institution of therapy was brief. On the evening of the third day in the hospital, penicillin, streptomycin, and chloramphenicol were given. Corticotropin (Armour) was instituted 24 hr. later and continued for 39 days, with a maximal dose of 25 mg. every six hours and a total dose of 2.5 gm. (Fig. 1). Generally increased pigmentation and acne of the face and shoulders occurred 12 days after corticotropin therapy was started. These side effects gradually subsided after its withdrawal. An eosinopenic response to adrenal stimulation was prompt and sustained. The red blood-cell counts remained low for 10 days and then steadily rose to normal over a four-week period. A marked reticulocyte increase, rising to 47% three weeks after corticotropin therapy had been started, accompanied the rising red-cell counts. The icterus index rapidly fell from 50 units to normal, with a corresponding decline in the serum bilirubin. The Coombs test became negative during treatment, and with one questionable exception remained so. The temperature gradually fell to normal during the first three weeks of hospitalization. Clinical improvement was evident after about one week of treatment. At the time of the most recent clinic visit, 10 months after the acute onset, no anemia or icterus was evident; the patient was in complete symptomatic remission, and her liver was no longer palpable.

Hematological Data on Woman Observed During Two Acute Episodes of Acquired Hemolytic Anemia

Time	Red Cell Count, x10⁶	Mean Corpuscular Volume, Cu. μ	White Cell Count, x10³	Reticulocyte %	Icterus Index, Units	Coombs Test	Differential Count	Comment
1st Hemolytic Episode—1947—Splenectomy and Streptomycin								
Admission	1.79	100	6.2	17	25	+++	Leukemoid	Normal fragility
10 days postoperative	1.80	112	9.0	27	32	.....	.....	.....
Discharge	4.07	120	8.7	3	10	.....	Not leukemoid	No HCl
Remission—1948								
Admission	3.49	106	9.6	..	..	.....	.....	Pregnant
2d Hemolytic Episode—1950—Corticotropin and Streptomycin								
Admission	1.18	102	38.9	7.0	50	+++	Leukemoid	Decreased fragility
Remission	4.50	94	7.2	0.5	7	Neg.	Not leukemoid	Mean corpuscular diameter 9 μ

Case 2.—This boy, 17 mo., was admitted to the Pediatric Service on March 13, 1950. He had been in good health until December, 1949, when cough and diarrhea developed. Urine, throat, and stool cultures failed to establish the etiology of these symptoms. He was hospitalized elsewhere for two months, receiving aureomycin, chloramphenicol, and one blood transfusion. The diarrhea subsided, and one month prior to admission here the red blood-cell count was reported as 4 million and the hemoglobin content as 12 gm. One week later the patient was readmitted with severe anemia, the red-cell count being 1,520,000 and the hemoglobin content 4 gm. The white-cell count was 17,000 and the marrow was erythroblastic. Repeated transfusions failed to maintain the blood-cell counts. Injections of liver and multivitamins were also administered.

On transfer to the Illinois Research and Educational Hospital, the patient weighed 20 lb. (9.1 kg.) and was seen to have pallor, anorexia, irritability, barely palpable spleen, and fever of 100.4 F. Lymph nodes and liver were not palpable. Jaundice was not evident. Purulent material was recovered from sinus washings. Escherichia coli grew out on several nose and throat cultures. There was a marked macrocytic anemia with a red-cell count of 1,700,000, a hemoglobin content of 6.5 gm., and a mean corpuscular volume of 123 cu. μ. The red cells showed anisocytosis, poikilocytosis, and polychromatophilia. Ten per cent of the red cells were reticulocytes, and there were three normoblasts per 100 white cells. The differential count of the blood smear was otherwise normal, and the white blood-cell count was 7,700. The Coombs test was strongly positive. The patient's blood type was A$_1$B, Rh$_1$Rh$_2$, with negative cold agglutinins and positive warm isoagglutinins in albumin but not in isotonic sodium chloride solution. Bleeding time, clotting time, icterus index, serum bilirubin, and urinary urobilinogen were within normal limits on admission. Fecal urobilinogen was elevated to 73 mg. per day, as opposed to normal values of 22 to 42 mg. in a child at his stage of development.

The patient's course in the hospital (Fig. 2) was characterized by recurrent bouts of fever, often to 102 but rarely to 104 F. During fever there was roentgenologic evidence of bilateral pneumonitis, more marked on the right. Partial remissions of this pneumonitis, in response to repeated courses of penicillin and aureomycin, were unaccompanied by any hematological benefit. His general condition remained poor. The liver and spleen gradually increased in size. He was given ferrous salts, vitamins, and repeated blood transfusions, at first with type AB, Rh-negative and later with type O, Rh-negative cells suspended in isotonic sodium chloride solution. A clinical, serologic, or hematologic remission was not achieved during five months of such management.

On Aug. 17, 1950, a course of 5 mg. of corticotropin (Wilson) three times daily was started, making a total course of 400 mg. in 26 days. The number of eosinophils was at first near zero but increased during the second half of the course and rose as high as 400 per cubic millimeter. Clinical side effects of corticotropin administration were evident, such as rounding of the face, increased skin pigmentation, and prominence of the abdomen. Clinical and laboratory improvement was rapid and dramatic: The liver and spleen decreased in size; red-cell counts increased rapidly; serum bilirubin and reticulocyte counts decreased toward normal, and there was diminished excretion of urinary and fecal urobilinogen. Results of the Coombs test, however, remained unaltered on repeated testings. The patient suffered a very severe attack of pneumonitis one week after corticotropin therapy had been discontinued. The hematological remission persisted for one month after this course of corticotropin, following which progressive relapse became evident.

A second course of 20 mg. of corticotropin (Wilson) daily for two weeks resulted in similar dramatic improvement. An attempt to maintain remission with use of 10 mg. of corticotropin three times weekly was unsuccessful, since the hemoglobin content dropped from 11.8 to 5.6 gm. in one week. A third course of 20 mg. of corticotropin daily for two weeks

again induced remission of the hemolytic anemia without change in the Coombs titer. Increased tendency toward bleeding from depression of the megakaryocyte count and thrombocytopenia became evident early in the third course of therapy. Because of toxic side effects, the drug was withdrawn, after which respiratory symptoms became increasingly severe and the chest

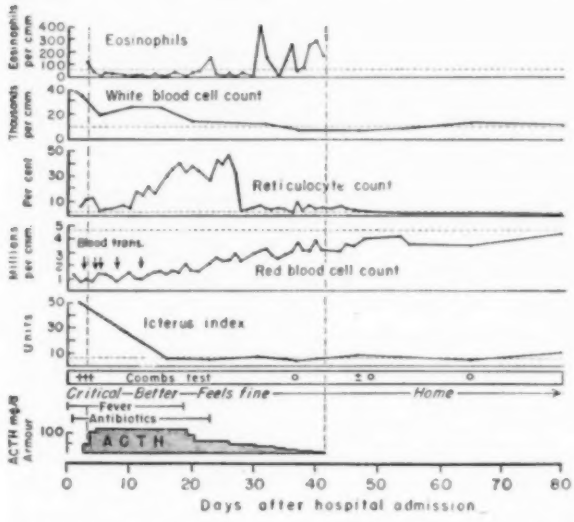


Fig. 1.—Data on a woman, 22, with second episode of acquired hemolytic anemia.

x-ray revealed almost complete consolidation. The patient died of the respiratory condition despite a fourth course of corticotropin. Principal autopsy findings included chronic interstitial pneumonitis of all lobes, chronic hyperplasia and hemosiderosis of the spleen, and marked normoblastic hyperplasia of the bone marrow.

COMMENT

Figure 3 illustrates probable mechanisms of hemolysis in acquired hemolytic anemia. Poorly understood circumstances promote the adsorption of globulins to the surface of red cells. Clinical observation suggests that such circumstances may include transfusion with cells of slight incompatibility, the presence of bacterial foci, or the coincidence of other hypersplenic diseases.[7]

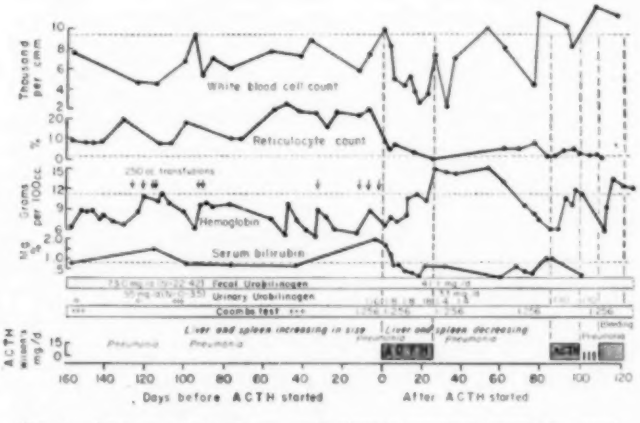


Fig. 2.—Data on a boy, 17 mo., with chronic acquired hemolytic anemia and chronic resistant pulmonary condition.

Reticuloendothelial cells, particularly of the spleen, are active in coating the red cells with this protein.[8] Such a coating is detected by the direct Coombs test, in which red cells washed in isotonic sodium chloride solution are incubated with antihuman globulin rabbit serum. Agglutination indicates a positive test. The amount of globulin present, as measured by the quantitative Coombs test, correlates roughly with the evident degree of hemolysis,[9] though occasional patients with weakly positive Coombs tests have no evident hemolysis.[7] Adsorption of certain abnormal globulins at the cell surface appears to increase mechanical fragility and shorten the life span of the erythrocyte. The cells are then more easily broken down by mechanical buffeting as they circulate through the capillary bed and are more susceptible to the destructive and phagocytic activity of the reticuloendothelial system. Secondary findings of hemolytic anemia arise from the increased breakdown of hemoglobin pigments and compensatory hyperplasia of the bone marrow.

The abnormal globulin which coats the red cells is probably an immune globulin, but this has yet to be proven. There are several theoretical mechanisms by which an immune globulin might involve the red cells. An antibody to an environmental allergen might, for some reason, become fixed to the cell surface. Hemolysis would then follow exposure to that antigen. The hemolytic anemia which, in sensitized patients, follows inges-

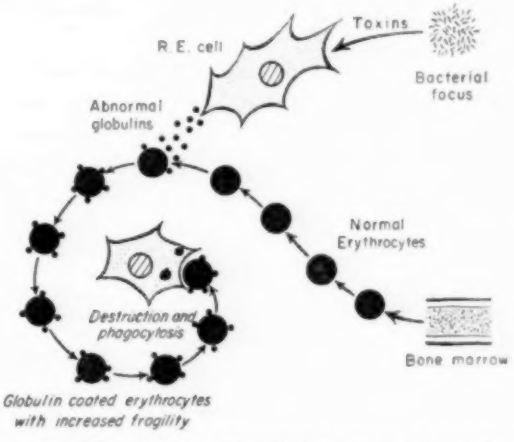


Fig. 3.—Probable mechanism of hemolysis in acquired hemolytic anemia. Under abnormal stimuli, such as the presence of certain toxins, reticuloendothelial cells form abnormal globulins which adhere to the surface of normal erythrocytes, causing increased fragility and predisposing them to premature destruction.

tion of the ripe fava bean or inhalation of its pollen probably represents this sort of a mechanism.[10] This reaction begins within hours after exposure, reaches a maximum in a few days, and subsides rapidly thereafter. Reactions to the Coombs test have not been studied in the reported cases of this disease. Acquired hemolytic anemia, on the other hand, is more chronic in its course and has no obvious allergic etiology.

7. Wright, C. S.; Dodd, M. C.; Bouroncle, B. A.; Doan, C. A., and Zollinger, R. M.: Studies of Hemagglutinins in Hereditary Spherocytosis and in Acquired Hemolytic Anemia: Their Relationship to the Hypersplenic Mechanism, J. Lab. & Clin. Med. **37**: 165 (Feb.) 1951.

8. Wagley, P. F.; Shen, S. C.; Gardner, F. H., and Castle, W. B.: Studies on Destruction of Red Blood Cells: The Spleen as the Source of Substance Causing Agglutination of the Red Blood Cells of Certain Patients with Acquired Hemolytic Jaundice by Antihuman Serum Rabbit Serum (Coombs' Serum), J. Lab. & Clin. Med. **33**: 1197 (Oct.) 1948.

9. Evans, R. S., and Duane, R. T.: Acquired Hemolytic Anemia: Relation of Erythrocyte Antibody Production to Activity of the Disease: The Significance of Thrombocytopenia and Leukopenia, Blood **4**: 1196 (Nov.) 1949.

10. Luisada, A.: Favism: A Singular Disease Chiefly Affecting the Red Blood Cells, Medicine **20**: 229 (May) 1941.

Red cells may also be coated on admixture with appropriate type-specific hemagglutinins giving a positive Coombs test. In erythroblastosis fetalis, for example, maternally produced anti-Rh antibodies cross the placenta and combine with the Rh antigen inherent in the fetal cell.[11] This hemolytic anemia differs from the acquired variety only in that the reaction is type-specific and the antired-cell antibody is externally produced. The hemolysis of transfusion reactions belongs in the same category as erythroblastosis.

The production of antibodies against a person's own red cells would constitute a very abnormal immunologic reaction. However, the formation of immune globulins directed against autogenous tissue has been postulated for other syndromes. It has been assumed, for example, that acute diffuse glomerulonephritis following acute infection might be the result of a bacterial toxin, renal protein complex which stimulates the formation of a specific antibody against the fixed antigen, the renal tissue.[12] In glomerulonephritis this antigen-antibody reaction would produce inflammatory and fibrotic reactions in the renal parenchyma. It is interesting though not conclusive in this regard that, as in glomerulonephritis, bacterial infection often precedes or accompanies acute hemolytic anemia.

If a bacterial toxin, red-cell stroma complex would stimulate production of antired-cell antibody, the combination of that immune globulin with the circulating erythrocytes could not produce inflammatory and fibrotic changes but might well result in premature destruction.

The observations that combination of these globulins with the red cells is enhanced at an acid hydrogen-ion concentration [13] or in rare cases by extreme depression of temperature (paroxysmal cold hemoglobinuria) [14] are related to the physicochemical properties of the proteins involved and carry no implications regarding their possible immunologic nature. As regards the first characteristic, it has been postulated that increasing carbon-dioxide tension during cellular stasis in the spleen might decrease the plasma hydrogen-ion concentration and promote the adsorption of globulins.

The activity of in vitro hemolytic systems is correlated with the concentrations of complement and magnesium in the serum.[15] The position of these factors in acquired hemolytic anemia has not been fully elucidated. If active, they might influence the course of the disease but would not be etiologically significant.

Whatever the nature of the adsorbed globulin, the action of corticotropin might be postulated as inhibiting its production or adsorption to the red cells. Such a mechanism appears active in those cases in which a progressive decrease in the Coombs titer can be demonstrated during therapy. Unfortunately we cannot interpret the reversal in the Coombs-test reactions in our first case as necessarily resulting from the action of corticotropin alone inasmuch as the patient had previously experienced a prolonged remission following use of streptomycin, an agent again administered during this episode. Her critical condition precluded trial of corticotropin therapy alone. The prompt response to streptomycin after two months of chronic hemolysis during her initial episode suggests that a bacterial focus might have nurtured the continued production of abnormal globulin at that time.

The adrenal corticoids stimulated by corticotropin would appear to increase the resistance of red cells to mechanical fragility despite a coating of globulin, as evident in the second case. Marked hematological remissions were repeatedly induced by corticotropin therapy with no significant alteration in the Coombs titer. Hemolysis returned each time the drug was withdrawn. The cell membrane has been proposed as an important site of corticoid activity in the response of a wide spectrum of diseases to corticotropin therapy.[16] The observations on this second case would tend to substantiate such an hypothesis.

SUMMARY

Two patients with acquired hemolytic anemia were treated with corticotropin (ACTH). Both experienced clinical and hematological remission within five to 10 days. Both had markedly positive Coombs test on admission. The first patient's test reaction became negative, and she remains in remission after 10 mo. Antibiotics may have been at least partially responsible for this remission. The second patient's test reaction did not change, and hemolysis returned within a month. Second and third remissions were induced by further courses of corticotropin. A chronic pulmonary condition, however, ultimately led to the patient's death. Corticotropin appears to increase resistance of the globulin-coated red cell to fragility. On the basis of our limited experience, we feel that this compound is a useful adjunct in the management of this syndrome.

1853 W. Polk St. (Dr. Best).

11. Jakobowicz, R.; Krieger, V. I., and Simmons, R. T.: Value of the Coombs Test in Detection of Isosensitization of the Newborn, M. J. Australia **2**: 143 (Aug. 7) 1948.

12. Lange, K.; Gold, M. M. A.; Weiner, D., and Simon, V.: Autoantibodies in Human Glomerulonephritis, J. Clin. Invest. **28**: 50 (Jan.) 1949.

13. Gardner, F. H.: Transfer to Normal Red Cells of Agglutinin Demonstrable in Acidified Sera of Patients with Acquired Hemolytic Jaundice, J. Clin. Invest. **28**: 783 (July) 1949.

14. Siebens, A. A.; Zinkham, W. H., and Wagley, P. F.: Observations on the Mechanism of Hemolysis in Paroxysmal (Cold) Hemoglobinuria, Blood **3**: 1367 (Dec.) 1948.

15. Mayer, M. M.; Osler, A. G.; Bier, O. G., and Heidelberger, M.: The Activating Effect of Magnesium and Other Cations on Hemolytic Function of the Complement, J. Exper. Med. **84**: 535 (Dec.) 1946.

Irradiation in Birthmarks.—The application of a beta radiation plaque is . . . the best way to treat a flat salmon patch capillary lesion except when this is so large that treatment would be inordinately protracted. Carefully used the plaque leaves no mark at all. It has the great merit that its use does not frighten young children since it is small, light, easily applied and does not necessitate the child lying still. These facts justify its use even for comparatively large lesions on some occasions. The inability of beta rays to penetrate the tissues restricts the use of the plaque . . . to superficial flat capillary lesions. . . . The use of gamma rays either as radon, radium or x-rays is absolutely contraindicated for birthmarks except possibly for a very large infiltrating cavernous lesion. . . . The tragedies of treating benign birthmarks with gamma rays are not fully appreciated since the ill-effects may not become apparent for many years. The growth of normal surrounding tissues is retarded in children and radiation dermatitis is unnecessarily risked at all ages. A growing epiphysis is especially easily damaged.—D. N. Matthews, M.D., Birthmarks and Moles, *Proceedings of Royal Society of Medicine*, July, 1951.

GASTROINTESTINAL COMPLICATIONS OF IRRADIATION FOR CARCINOMA OF UTERINE CERVIX

Edwin F. Aune, M.D.
and
Benjamin V. White, M.D., Hartford, Conn.

Gastrointestinal injury following irradiation was first described by Walsh [1] in 1897. He cited the case of a man working with x-rays in whom diarrhea developed after several weeks' exposure. During a two-month vacation the symptoms subsided, only to recur on subsequent re-exposure. Buie and Malmgren [2] in 1930 were the first to use the term "factitial proctitis" to irradiation injury of the rectum. They described the pathological changes observed in the walls of the rectum after the use of radium in the treatment of cervical carcinoma. Since that time numerous authors [3] have reported on the incidence of such changes following radiation therapy of the cervix.

Nausea occurs so frequently immediately after radiation that this symptom is often known as radiation sickness, but it is usually self-limited and causes little diagnostic confusion. The symptoms caused by structural injury to the intestine, on the other hand, are quite variable, and their significance may be difficult to recognize. In order to evaluate the incidence of such complications following radiation therapy and their diagnostic features, a study was undertaken of 670 patients treated in the Gynecological Tumor Clinic of the Hartford Hospital from Jan. 1, 1938, through Dec. 31, 1949.

MATERIAL AND METHOD OF TREATMENT

In 1938, radium needles supplanted the tandem tubes and bombs previously employed. Since that time radium needles have been used in conjunction with x-ray therapy as the standard treatment for carcinoma of the cervix. There were 540 cases treated in this manner. In an additional 95 cases x-ray therapy was used alone, and 35 cases were treated with radium needles alone. The dosage of radium varied with the individual patient from 4,000 to 8,000 mg.-hr. and that of x-ray therapy from 6,000 to 12,000 r.

In every instance a successful follow-up for six months or longer was obtained. In most instances this was accomplished by visits of the patients to the clinic, but in a few cases information was obtained from physicians. Follow-up notes were consistently made on the Tumor Clinic records and were available for study.

INCIDENCE OF COMPLICATIONS

Of 670 patients treated for cervical carcinoma between Jan. 1, 1938, and Dec. 31, 1949, thirty-four (5.07%) experienced definite complications, most of which involved the gastrointestinal tract (Table 1). The incidence of gastrointestinal complications was 3.4%. This figure is lower than that of Todd [3a] (5%, Ahumada and Chevalier [3b] (4.48%), Chydenius [3c] (10.2%), and Corscaden, Kasabach and Lenz [3d] (8.7%), but it exceeds that of Buie and Malmgren [2] (3.0%).

The gastrointestinal complications fell into two general groups: ileal, and rectosigmoid. There were 6 cases of ileitis (26.1%) and 17 cases of proctosigmoiditis (73.9%). The incidence of ileitis was higher than that encountered by Corscaden, Kasabach and Lenz [3d] (10.2%), and that quoted by Pessel [4] (9.0%). Among the 23 cases with gastrointestinal complications there were three deaths, all of them caused by perforation of a radiation ulcer, two in the rectosigmoid and one in the ileum. The over-all fatality rate from gastrointestinal complications was, therefore, 0.4%, a much lower figure than that of Morton and Kerner [5] (3.7%).

CLINICAL FEATURES

The symptoms of radiation injury to the ileum or rectosigmoid may appear within the first month after the institution of therapy, or as late as nine years afterward. These symptoms fall into two general groups: (1) those pointing to proctosigmoiditis; and (2) those indicative of mechanical intestinal obstruction. With proctosigmoiditis the symptoms may be either colitic or obstructive, but with ileitis obstructive symptoms are the rule (Table 2). Generally colitic symptoms make their appearance within the first seven months after onset of treatment, whereas obstructive manifestations are seldom encountered before the fifth month and may not be noted for several years (Fig. 1).

TABLE 1.—*Number of Patients Treated for Carcinoma of the Cervix and Incidence of Complications*

Total patients treated from 1938 to 1949..... (100% followed for 6 mo. or longer)	670
Total complications of radiation.....	34
Gastrointestinal	23
Genitourinary (cystitis).....	7
Fractures of femur.....	3
Rectovaginal fistula.....	1

Colitic symptoms usually consist of tenesmus and diarrhea accompanied with the passage of blood-stained mucus. In severe cases there may be frank bleeding with the passage of clots (Table 3). On sigmoidoscopic exam-

Resident in medicine, Hartford Hospital (Dr. Aune).

From the Gynecological Tumor Clinic and the Medical Service of the Hartford Hospital.

Assistant Professor of Clinical Medicine, Yale University School of Medicine; Assistant Visiting Physician, Hartford Hospital (Dr. White).

1. Walsh, D.: Deep Tissue Traumatism from Roentgen-ray Exposure, Brit. M. J. **2**: 272 (June) 1897.

2. Buie, L. A., and Malmgren, G. E.: Factitial Proctitis: A Justifiable Lesion Observed in Patients Following Irradiation, Internat. Clin. **3**: 68 (Sept.) 1930.

3. (*a*) Todd, T. F.: Rectal Ulceration Following Irradiation Treatment of Carcinoma of the Cervix, Surg., Gynec. & Obst. **67**: 617 (Nov.) 1938. (*b*) Ahumada, J. C., and Chevalier, R. M., cited by Bockus, H. L., and others: Gastro-Enterology: The Small and Large Intestine and Peritoneum; Diagnosis and Treatment of Disorders of Small Intestine, Colon, Peritoneum, Mesentery and Omentum, vol. 2, Philadelphia, W. B. Saunders Company, 1944, p. 797. (*c*) Chydenius, J. J.: Lesions of Rectum Due to Radium Therapy of Cancer of Uterus, Nord. Med. (Finska läk.-sällsk. handl.) **11**:2595 (Sept. 13) 1941. (*d*) Corscaden, J. A.; Kasabach, H. H., and Lenz, M.: Intestinal Injuries After Radium and Roentgen Treatment of Carcinoma of the Cervix, Am. J. Roentgenol. **39**: 871 (June) 1938.

4. Pessel, J. F.: Factitial Proctitis, in Bockus, H. L., and others: Gastro-Enterology: The Small and Large Intestine and Peritoneum; Diagnosis and Treatment of Disorders of Small Intestine, Colon, Peritoneum, Mesentery and Omentum, vol. 2, Philadelphia, W. B. Saunders Company, 1944, p. 797.

5. Morton, D. G., and Kerner, J. A.: Reactions to X-Ray and Radium Therapy in Treatment of Cancer of Uterine Cervix, Am. J. Obst. & Gynec. **57**: 625 (April) 1949.

ination in the first weeks after treatment the mucosa is red, edematous, and friable. Later, the mucous membrane becomes atrophic with multiple telangiectases, and scar tissue contraction may be noted. When an ulcer is present, it is oval or circular with discrete heaped-up or indurated margins, which on digital examination feel like carcinoma. The base of the ulcer is gray and may contain fibrin clots. Multiple ulcers are occasionally noted. Ulcers of this type sometimes perforate and lead to peritonitis as in the following case.

TABLE 2.—*Predominant Symptoms of Proctosigmoiditis and Ileitis Due to Radiation Injury (34 Cases)*

	Proctosigmoiditis	Ileitis
Colitic symptoms	15	0
Obstructive symptoms	2	6

REPORT OF CASES

CASE 1.—N. M., a white married woman aged 38, in September, 1949, noted the onset of vaginal bleeding caused by epidermoid carcinoma of the cervix, grade II, stage II-III. On Oct. 7, four 3-mg. parametrial needles, eight 2-mg. paracervical needles, and two 10-mg. capsules were inserted and kept in place for one week. The total dose was 8,064 mg.-hr. Soon thereafter moderately severe and persistent diarrhea developed accompanied with tenesmus, lower adbominal crampy pain, weakness, and debility, with a loss of 40 to 50 lb. (18.1 to 22.7 kg.) in weight. Because of inability to control the symptoms, she was hospitalized. Physical examination revealed a thin, chronically ill woman with definite tenderness in the left lower quadrant. A barium enema on March 1 showed spasm and marked narrowing in the region of the rectosigmoid. Because of severity of diarrhea, a colostomy was performed to divert the fecal stream. Two days later the colostomy was opened. That afternoon the patient suddenly went into shock and, in spite of supportive therapy, rapidly became worse and died the following morning.

At autopsy there were collections of feculent fluid in Morison's pouch, in the left upper quadrant, and in the pelvis. There was fibrinopurulent exudate over the serosa of the entire small bowel. The junction of the sigmoid and rectum was markedly thickened by chronic inflammation. At a point on the anterior surface of the rectosigmoid just above the peritoneal reflexion and posterior to the uterus, there was an area of ulceration measuring 6 cm. in diameter with a 3-cm. perforation in its center (Fig. 2). A section taken from the vagina near the cervix and an iliac node showed metastatic epidermoid carcinoma. A section of the rectosigmoid showed extensive ulceration and complete absence of the mucosa, but no evidence of tumor.

TABLE 3.—*Symptoms Encountered in Patients with Ileal Involvement and in Those with Proctosigmoiditis*

Symptoms	Ileal Disease (6 cases)	Rectosigmoid Disease (17 cases)
Obstructive		
Cramps	6	9
Nausea	6	4
Vomiting	5	3
Distention	5	4
Colitic		
Diarrhea	1	16
Passage of mucus	1	16
Passage of blood	1	12
Tenesmus	0	12
Perforation of colon	0	2

With obstructive symptoms the manifestations are usually those of a mechanical ileus with abdominal distention, cramplike pain, nausea, vomiting, and obstipation (Table 3). The pain is characteristically midabdominal, is brought on immediately after ingestion of food, and is not relieved by antacids or antispasmodics. Often the abdomen is tympanitic, and high-pitched, audible peristalsis can be made out. The next case represents primarily obstructive manifestations with subsequent fatal outcome owing to perforation of gangrenous ileal loops.

CASE 2.—E. B., a white married woman aged 41, had a biopsy of the cervix in November, 1948, because of a slight watery, pink, vaginal discharge of four to five months' duration. The biopsy revealed epidermoid carcinoma of the cervix, grade II. The following day, four 3-mg. radium needles, seven 2-mg. needles and two 10-mg. capsules were inserted and left in place for one week for a total dose of 7,728 mg.-hr. This was followed by a course of deep x-ray therapy given over a period of 25 days for a total dose of 6,000 r. Three months after the completion of the irradiation, the patient began to have generalized crampy lower abdominal pains. These gradually became more frequent and severe, and occasionally were associated with a bloody mucoid diarrhea. In the latter part of May, 1949, sigmoidoscopy showed strings of bloody mucus coming from above a constriction of the bowel at about 15 cm., but a gastrointestinal series and barium enema were negative. The following month another barium enema with air contrast was performed, and during this procedure the patient experienced severe abdominal pain. This pain persisted, and the patient was admitted to the Hartford Hospital five days later. For 36 hours before admission the patient had had no bowel movements, and she had vomited some fecal smelling material. The abdomen was distended, and loud, high-pitched peristaltic sounds were audible. There was tenderness over the lower abdomen, most marked in the left lower quadrant. Pelvic examination revealed both vaults to be fixed, and a mass was felt on the left. A flat plate of the abdomen showed the entire midabdomen to be filled with loops of small bowel which were partially distended producing a "step-ladder" configuration. A Miller-Abbott tube resulted in marked improvement. The distention was relieved and the abdominal cramps subsided. On the third hospital day a barium suspension was introduced into the Miller-Abbott tube and films taken. These showed the mucosal outline of the ileal loops to be grossly irregular, suggesting a diffuse ileitis (Fig. 3). On the 10th hospital day the Miller-Abbott tube was removed. At that time the patient was having normal bowel movements and the abdomen was no longer distended. Three days later she was discharged with the instructions to follow a soft, low-residue diet and to report the development of further symptoms. Discharge diagnoses were: (1) carcinoma of the cervix, treated; (2) postradiation enteritis, and (3) subacute intestinal obstruction.

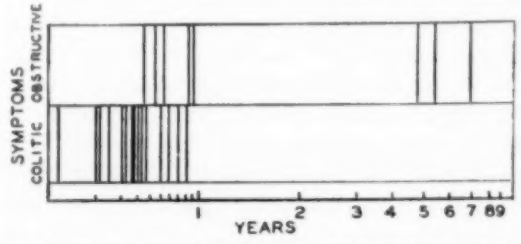


Fig. 1.—Time of onset of symptoms in radiation injury of the gastrointestinal tract. Colitic symptoms make their appearance within the first year, but obstructive symptoms may occur extremely late.

The patient did well until about one month later, when she again began to have severe crampy lower abdominal pains associated with constipation. The pain increased in severity, and five days later she was readmitted to the hospital. Twenty-four hours prior to admission the patient became disoriented, incontinent of urine, and gradually lapsed into a coma. On admission to the hospital she was semistuporous and markedly dehydrated. The blood pressure was 90/55, temperature 103 F., pulse 128, and respirations 24. The abdomen was distended and tympanitic with marked tenderness to palpation throughout. Peristaltic sounds were absent. After admission the patient became progressively worse and died the next morning.

At autopsy the peritoneal cavity contained about 2 l. of purulent fluid. There was an exudate over the parietal and

visceral peritoneal surfaces. There were many fibrinous adhesions, and several loops of terminal ileum were adherent in the cul-de-sac to the posterior uterine wall. One loop was definitely necrotic, and there were several 3 to 4 mm. perforations. This loop was about 15 cm. from the ileocolic valve (Fig. 4). The sigmoid was markedly thickened, contracted, and stenotic, and was adherent to the left cornu of the uterus. There was marked fibrinous thickening of the perirectal tissues. On examination the cervix was very small, atrophic, and stenotic, and without any evidence of remaining tumor tissue. The other organs were all normal except for a moderate right hydro-ureter.

PATHOLOGY

The intestinal mucosa is unusually susceptible to damage from irradiation. Cutler [6] stated that the rectal mucosa is one of the most sensitive tissues in the body to the effects of x-ray. This fact, plus the close proximity of the rectum and sigmoid to the cervix and uterus, probably accounts for the high incidence of irradiation injury in this portion of the gastrointestinal tract. According to Pessel [4] the sigmoid is involved in 47% of cases, the rectum in 28%, both rectum and sigmoid in 14%, and the ileum in 9%. MacIntosh and Hutton [7] found the

Fig. 2 (case 1).—Specimen showing perforation of the anterior surface of the rectosigmoid.

ileum to be damaged in six out of 44 irradiation injuries. The large bowel injuries in their cases were limited to the sigmoid and rectum, and the greatest number of injuries were in the distal sigmoid or in the rectosigmoid junction.

The earliest pathological change that takes place after irradiation injury of the bowel is an acute inflammatory reaction with edema, hyperemia, and spasm. This change may occur at any time during the latter part of the course of therapy, or one to two weeks after completion of the treatment. It may subside without further complications. In more serious cases there may be primary injury to the blood vessels with endarteritis, thrombosis, and subsequent infarction of the involved area of bowel. The mucosa may then ulcerate, leaving confluent single or multiple irregular superficial erosions which progress to deep, punched-out, discrete ulcers with grayish ragged bases and sharp margins. The surrounding mucosa may become thickened and indurated, and numerous telangiectases may form. If an ulcer perforates into the peritoneal cavity, generalized peritonitis usually ensues. If the ulcer perforates into the vagina, a rectovaginal fistula may form, or if the perforation takes place into the perirectal tissues, an ischiorectal abscess may develop.

A later pathological change is the formation of varying amounts of fibrous tissue. As the lesions heal, bands of scar tissue may constrict the bowel and produce obstruction. In some cases the primary irradiation injury may involve the perirectal tissues, with subsequent pro-

Fig. 3 (case 2).—X-ray taken after introduction of barium suspension through Miller-Abbott tube showing irregularity of ileal loops.

duction of a diffuse mass of fibrous tissue involving all pelvic structures and producing a condition difficult to differentiate from a frozen pelvis caused by extension of carcinoma. Todd [3n] terms this latter change "extrinsic" injury as opposed to the "intrinsic" injury which is confined to the mucosa and wall of the intestine itself.

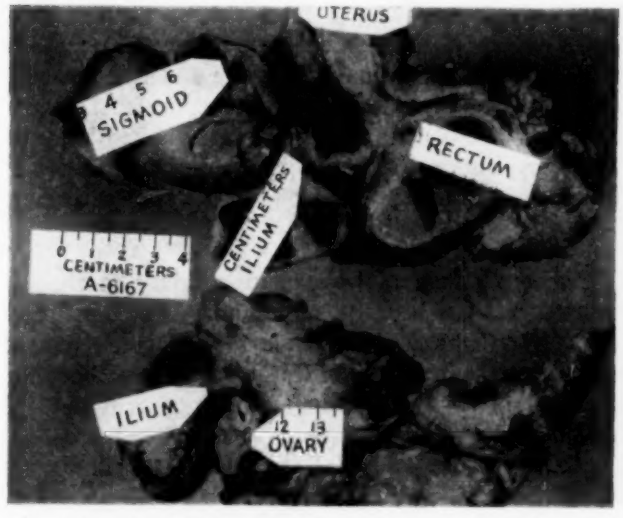


Fig. 4 (case 2).—Specimen showing necrotic ileal loop with perforations.

DIFFERENTIAL DIAGNOSIS

In many cases the diagnosis of irradiation injury of the bowel is fairly obvious. It should be considered in any patient with a history of treatment of carcinoma of

6. Cutler, M.: Complications of Radio-Therapy in Cancer of Cervix, Surg., Gynec. & Obst. 74: 867 (April) 1942.

7. MacIntosh, H. C., and Hutton, J. E.: Clinical and Roentgen Aspects of Irradiation Stricture of Rectum and Sigmoid: Its Course and Treatment, Am. J. Roentgenol. 52: 647 (Dec.) 1944.

the cervix by radium or x-ray, in whom symptoms related to the intestinal tract, such as obstruction, tenesmus, abdominal pain, diarrhea, or rectal bleeding subsequently developed. In cases in which the injury is limited to the rectum and lower sigmoid, the diagnosis can usually be made on sigmoidoscopy, as the appearance of the bowel is quite characteristic, especially if telangiectases are present. In occasional cases, however, it may be difficult to determine whether or not one is dealing with a recurrence or with extension of the cervical carcinoma. Where there has been considerable perirectal fibrous tissue formation, a picture similar to a so-called "frozen pelvis" may develop. At times a rectal ulcer may feel very much like carcinoma. Other conditions to be differentiated are amebic and bacillary colitis, ulcerative colitis, diverticulitis, and functional bowel disturbances.

TREATMENT

In the large majority of instances treatment is conservative. Irradiation injury is usually self-limited, and the symptoms can be controlled by palliative means. A low-residue diet is invariably indicated. The use of antispasmodics and sedatives is helpful. Rectal instillations of starch water or warm oil are soothing to the irritated bowel. In cases where there is troublesome rectal bleeding, a solution of 1% tannic acid as a 6 ounce retention enema is useful.

When obstructive symptoms with frequent vomiting develop, hydration and maintenance of electrolyte balance are important. Transfusions of blood or plasma may occasionally be indicated. In some cases a Miller-Abbott tube may be effective in relieving the obstruction. If the patient does not respond to medical treatment, surgery is necessary. Aldridge [8] pointed out that surgery might be indicated to (1) relieve pain, bleeding, and partial or complete intestinal obstruction; (2) remove necrotic bowel which may perforate; and (3) promote healing of ulcerative lesions by diverting the fecal stream. The operation of choice in most cases is ileostomy or colostomy, although if necrotic bowel or perforation is present, resection with anastomosis may be necessary.

COMMENT

The importance of postradiation injury to the intestinal tract has been of interest to gynecologists and radiologists, whose efforts have been directed toward minimizing the incidence of this complication. Since the intestinal mucosa is unusually susceptible to damage from irradiation, it is sometimes quite difficult to deliver a sufficient amount of radiation to destroy the malignant process and still prevent excessive, harmful, secondary irradiation effects from developing in adjacent structures, principally the rectosigmoid and ileum. Overdosage and faulty technique are frequent causes of irradiation injury. There are reports of injury caused by accidental dislodgement of radium applicators from the cervical canal or uterine cavity into the vagina. Other conditions resulting from excessive exposure of the intestines to irradiation include retroverted uterus, uterus with a thin muscle wall, and peritoneal adhesions fixing one or more loops of intestines in the pelvis where they are apt to receive a concentrated dose of irradiation. Tissue tolerance may be reduced by poor general health and by degenerative diseases. Both Martin [9] and Aldridge [8] have described ways to reduce irradiation injury of the gastrointestinal tract in treatment of carcinoma of the cervix. These include changes of technique in applying radium, procedures to prevent accidental dislodgement of radium applicators from the cervical canal and uterine cavity, caution in the use of irradiation in treating patients who have had pelvic infections or previous abdominal or pelvic operations, and gastrointestinal series prior to irradiation to determine whether any loops of the bowel are adherent to the uterus or cervical stump.

However, there have been few articles in the literature on internal medicine stressing the clinical syndromes oftenest encountered or their diagnostic features. Irradiation injury to the rectosigmoid and ileum is more common than realized, and the differential diagnosis is not always obvious. In fact, irradiation injury is often confused with recurrence of the malignant process. The so-called pseudocarcinoma of Todd [3a] is a radiation ulcer, which both looks and feels like fungating ulcerative cancer. Late radiation effects often produce induration in the perirectal tissues and vaginal vaults, which is difficult to differentiate from the malignant "frozen pelvis." Small bowel ileus is almost invariably assumed to be neoplastic in origin after a history of cervical carcinoma. Thus an occasional opportunity to help a patient is missed because the symptoms are interpreted as those of a hopeless intra-abdominal recurrence, when actually the primary disease is completely eradicated. For these reasons it seems desirable to re-emphasize the importance of radiation effects in diagnostic problems in the practice of the internist as well as complications in that of the gynecologic oncologist.

SUMMARY

A follow-up study was made of 670 patients treated by radiation techniques for carcinoma of the uterine cervix to determine the incidence of gastrointestinal complications and their clinical features.

The large number of individuals with transient "radiation sickness" were omitted from consideration.

Twenty-three patients had evidence of frank injury, 17 to the mucosa of the rectosigmoid and six to the ileum.

Most of the patients with involvement of the rectosigmoid had predominantly colitic symptoms, such as tenesmus, diarrhea, and the passage of blood by rectum. A few had evidence of mechanical ileus owing to scarring or edema.

All patients with ileal injury were recognized because of evidence of small bowel obstruction, i. e., distention, colic, nausea, vomiting, or obstipation.

There were three fatalities from peritonitis secondary to the perforation of radiation ulcers. Two of these cases are presented in detail.

85 Jefferson St.

8. Aldridge, A. H.: Intestinal Injury Resulting from Irradiation Treatment of Uterine Carcinoma, Am. J. Obst. & Gynec. **44**: 833 (Nov.) 1942.
9. Martin, C. L.: Elimination of Irradiation Injuries in Treatment of Carcinoma of Cervix, Am. J. Roentgenol. **49**: 494 (April) 1943.

ACUTE IDIOPATHIC PERICARDITIS

Commander Ralph C. Parker Jr., (MC) U. S. N.
and
Lieutenant Commander Henry R. Cooper,
(MC) U. S. N., Bethesda, Md.

Pericarditis is almost uniformly secondary to some other pathological process. It is usually an acute inflammation of the pericardium and subepicardial myocardium, with or without effusion, and its prognosis most often depends on the causative agent or underlying disease. The subsequent development of adhesive or constrictive pericarditis is always to be considered.

Smith and Willius [1] in 1932 found the over-all incidence of pericarditis to be 4.2% (373 cases) in 8,912 necropsies. Of this 4.2%, 38.4% had adherent pericarditis, whereas acute pericardial disease was present in 58%. More recently, Griffith and Wallace [2] reviewed 13,353 consecutive autopsies at the Los Angeles County Hospital and found 729 cases of pericarditis, an over-all incidence of 5.4%. In this latter series nonspecific idiopathic had the highest incidence of the acute inflammatory types, with rheumatic pericarditis also being high in frequency. They concluded that there has been a definite decrease in the incidence of tuberculous and pneumonic pericarditis. According to the textbooks, the six most frequent causes of acute pericarditis are rheumatic fever, pneumococcal infections, tuberculosis, uremia, myocardial infarction, and trauma.[3] In addition it has been found associated with upper respiratory infections,[4] allergy,[5] lymphogranuloma venereum,[6] primary atypical pneumonia,[7] rheumatoid arthritis,[8] myxedema,[9] tularemia,[3] measles, amebiasis,[10] influenza,[11] disseminated lupus erythematosis,[12] cancer, and many other diseases.

Since the widespread recognition of primary atypical pneumonia and the increased use of the electrocardiograph, particularly of multiple precordial leads, the detection and recognition of acute pericarditis associated with pneumonitis and upper respiratory infections has become more important. The association of acute pericarditis with upper respiratory infections has been known for several years. In 1934, Willius held a clinic on acute serofibrinous pericarditis secondary to acute pharyngitis.[4] However, this association received more widespread recognition with the publication of Barnes and Burchell's 14 cases in 1942.[13] Since then, several excellent case reports and case series have been published.[14]

The terminology for this clinical syndrome has not been resolved but, as pointed out by Burchell [12] in his classic review of this condition, in 1947, most phrases describe the acute aspect, probable varied etiology, relatively high incidence in young adults, tendency to relapse, and association with upper respiratory infections and pneumonitis. Burchell prefers the term "acute nonspecific" but has also suggested "acute relapsing" pericarditis. We use the term "acute idiopathic pericarditis" for, although the causative agent may be varied, the true etiology is unknown.

As this entity is often confused with other causes of acute chest pain, particularly coronary occlusion, and also with the more prognostically severe forms of pericarditis and myocarditis, its early recognition is important. In addition, there is now a possibility that the newer antibiotics will favorably influence the sometimes protracted course of the disease.

REPORT OF CASES

Of the four following abstracts illustrative of this disease, the first two cases (12 and 18) were considered "severe" and the other two cases (3 and 7) "mild" or "moderate." In the total of 22 cases the process was considered to be "severe" in four, "moderate" in 14, and "mild" in four (Fig. 1).

CASE 12.—M. A. C., a 27-yr.-old man, was admitted to the hospital on April 19, 1948, complaining of cough, pain in the right part of the chest, and shortness of breath of six days' duration. These symptoms were preceded by fatigue, malaise, low back pain, and insomnia. Sulfonamide compounds had been taken for about four days. The cough was productive of small amounts of white sputum. Examination showed an apprehensive man with a temperature of 100 F. and warm, moist skin. There were dimin-

From the Cardiology Department, United States Naval Hospital, National Naval Medical Center.

1. Smith, H. L., and Willius, F. A.: Pericarditis: Chronic Adherent Pericarditis, Arch. Int. Med. **50**: 171 (Aug.) 1932; Pericarditis: Calcification of Pericardium, ibid. **50**: 184 (Aug.) 1932; Pericarditis: Fibrinous Pericarditis and "Soldier's Patches," ibid. **50**: 410 (Sept.) 1932.

2. Griffith, G. C., and Wallace, L.: Etiology of Pericarditis, read before the Third Inter-American Cardiological Conference, Chicago, June, 1948.

3. Cecil R. L.: Textbook of Medicine, ed. 7, Philadelphia, W. B. Saunders Company, 1948, p. 1159.

4. Willius, F. A.: Cardiac Clinics: Clinic on Acute, Serofibrinous Pericarditis Secondary to Acute Pharyngitis; Comment; Treatment; Course, Proc. Staff Meet., Mayo Clin. **9**: 637, 1934.

5. McKinlay, C. V.: Allergic Carditis, Pericarditis and Pleurisy: Report of Case of Serum Sickness with Predominant Cardiac Manifestations and Symptomatic Recovery (Preliminary Report), Journal Lancet **68**: 61, 1948.

6. Sheldon, W. H.; Wall, M.; Slade, J. R., and Heyman, A.: Lymphogranuloma Venerum of Supraclavicular Lymph Nodes with Mediastinal Lymphadenopathy and Pericarditis, Proc. Am. Federation Clin. Res. **4**: 48, 1948.

7. Finkelstein, D., and Klainer, M. J.: Pericarditis Associated with Primary Atypical Pneumonia, Am. Heart J. **28**: 385, 1944.

8. Graef, I.; Hickey, D. V., and Altmann, V.: Cardiac Lesions in Rheumatoid Arthritis, read before the Seventh International Congress on Rheumatic Diseases, New York, May 30 to June 3, 1949, p. 69.

9. Harrell, F. T., and Johnston, C.: Pericardial Effusion in Myxedema, Am. Heart J. **25**: 505, 1943.

10. Carter, M. G., and Kornes, S. B.: Amebic Pericarditis, New England J. Med. **242**: 390, 1950.

11. Kresky, P. J.: Suppurative Pericarditis Due to Haemophilus Influenzae, Type B.: Characteristic Syndrome Ushered in by Symptoms of Croup, Am. J. Dis. Child. **65**: 305 (Feb.) 1943.

12. Burchell, H. B.: Acute Nonspecific Pericarditis, Mod. Concepts Cardiovas. Dis. **16**: [n.p.] 1947.

13. Barnes, A. R., and Burchell, H. B.: Acute Pericarditis Simulating Acute Coronary Occlusion: Report of 14 Cases, Am. Heart J. **23**: 247, 1942.

14. (*a*) Finkelstein and Klainer.[7] (*b*) Fuller, C. C., and Quinlan, J. W.: Acute Pneumonitis and Pericarditis: Report of Case, New England J. Med. **229**: 399, 1943. (*c*) Levy, R. L., and Patterson, M. C.: Acute Serofibrinous Pericarditis of Undetermined Cause: Study of 27 Cases, Am. J. Med. **8**: 34, 1950. (*d*) Logue, R. B., and Wendkos, M. H.: Acute Pericarditis of Benign Type, Am. Heart J. **36**: 587, 1948. (*e*) Nathan, D. A., and Dathe, R. A.: Pericarditis with Effusion Following Infections of Upper Respiratory Tract, ibid. **31**: 115, 1946. (*f*) Smalley, R. E., and Ruddock, J. C.: Acute Pericarditis: Study of 18 Cases Among Service Personnel, Ann. Int. Med. **25**: 799, 1946. (*g*) Talmage, W. G.: Acute Benign Pericarditis: Report of 2 Cases in Young Adults, Am. Heart J. **29**: 623, 1945. (*h*) Taubenhaus, M., and Brams, W. A.: Treatment of Acute Nonspecific Pericarditis with Aureomycin, J. A. M. A. **142**: 973 (April 1) 1950.

ished breath sounds at both lung bases and limitation of respiratory chest motion bilaterally. There were no other pertinent physical findings.

Laboratory work on admission yielded no remarkable findings except for a leukocyte count of 34,750 with 78 polymorphonuclear cells, 11 lymphocytes, 8 monocytes, and 3 eosinophils. A blood culture was later reported negative, and sputum examinations showed no pathogenic organisms. The temperature rose on the second day to 102 F and the respiratory rate to 28. An x-ray of the chest was compatible with atypical pneumonia involving the right lung. The heart was enlarged 18% by standard tables. On the third hospital day the patient complained of pain in the anterior chest, and a loud pericardial friction rub was heard. A standard lead electrocardiogram showed minimal ST elevations in leads 1 and 2. Further blood cultures were later reported negative.

On the sixth hospital day, because of the severity of the illness, a therapeutic trial of penicillin was instituted and maintained for seven days without response. By the 10th hospital day the leukocyte count had dropped to 8,750. An x-ray of the chest showed a homogenous increase in density from the second rib on the right to the diaphragm and a small collection of fluid in the right costophrenic angle. Two weeks after admission there was a relapse with increased temperature and a small hemoptysis. This

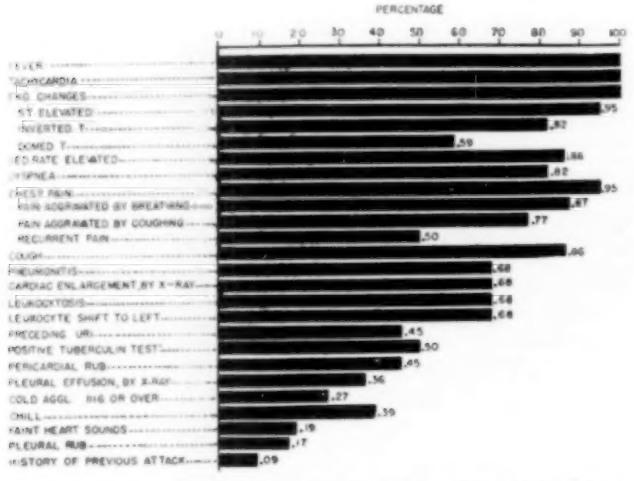


Fig. 1.—A chart showing the course of the disease in 22 cases. "Fever" refers to 100 F. or above. "Tachycardia" refers to a heartbeat of 100 or above. "Sed. rate" (Cutler) indicates 10 mm. or more in 60 min. "Leukocytosis" indicates 10,000 leukocytes per cubic millimeter or more. "Preceding URI" indicates upper respiratory infection preceding evidence of pericarditis by a few hours to two or three weeks. "History of Previous Attack" refers to a similar episode with apparently significant chest pain. "Pneumonitis" indicates the presence of disease as evidenced by x-ray, except for one or two instances. "Age of Patient" indicates ages ranging from 19 to 45. The average age was 32.

lasted about five days. The pericardial friction rub disappeared after the 21st day, and the electrocardiographic tracings returned to normal.

X-ray examination of the chest yielded normal findings on the 51st hospital day. However, on the 54th day the patient began to run a fever, which lasted eight days, and an area of pneumonitis appeared in the left lung and then slowly cleared. The tuberculin test was negative. He was discharged to his home on the 68th hospital day.

CASE 18.—G. J. D., a 35-yr.-old man, was admitted July 25, 1949, complaining of chest pain of eight hours' duration that started as a feeling of tightness in the neck and then spread to become substernal pain. The pain, dull in character, was aggravated by bodily movements, attempting to cough, or by taking a deep breath. Later he noticed dyspnea on attempting to lie flat, and he felt feverish. Examination showed an acutely ill, orthopneic, normally developed man. There was generalized, marked limitation of chest movement, depressed breath sounds over the right lower lobe of the lung and both coarse and fine inspiratory rales. At the cardiac apex a faint friction rub could be heard.

Admission laboratory studies showed a leukocyte count of 10,600 with 85% neutrophils and 15% lymphocytes, and a sedimentation rate of 24 mm. in an hour. An x-ray of the chest showed a 20% enlargement by standard tables in the transverse diameter of the heart, and clear lung fields. An electrocardiogram showed elevated ST segments in all limb leads and in V-4, 5, and 6 of the precordial leads. Blood cultures were later reported as negative.

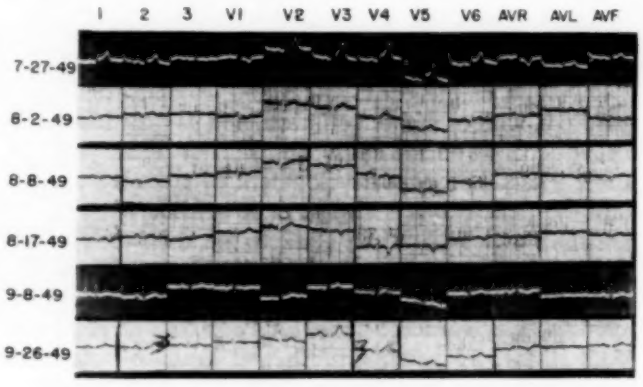


Fig. 2.—Temperature chart of G. J. D., Case 18.

After five days of observation, during which time the temperature remained between 100 and 101 F. with comparable pulse rate, increased respiratory rate, increasing cardiac enlargement, and persisting chest pain, penicillin was started. There was no response to five days of penicillin therapy, so this was discontinued and aureomycin hydrochloride, 2 gm. daily, was started. The electrocardiograms, meanwhile, had begun to show T wave inversions, the lung fields remained clear, and a tuberculin test was positive. Three days after aureomycin therapy was initiated the temperature fell to normal, and five days after start of this treatment the friction rub disappeared. The pain subsided and the patient felt progressively better (Figs. 2 and 3).

CASE 3.—L. J. L., a 20-yr.-old man, was awakened two and one-half days prior to admission on Jan. 18, 1946, by dyspnea and a dull ache in the precordial region and between his shoulder blades. The precordial pain had persisted, and he was forced to sit or stand because of dyspnea on lying down. Examination showed a pulse rate of 146 and respirations of 27. He was very apprehensive and slightly dyspneic. There were a few fine rales at both lung bases, the pulse was weak and the heart enlarged 3 cm. to the left of the midclavicular line. His skin appeared cyanotic, and he frequently coughed up frothy, slightly blood-tinged sputum.

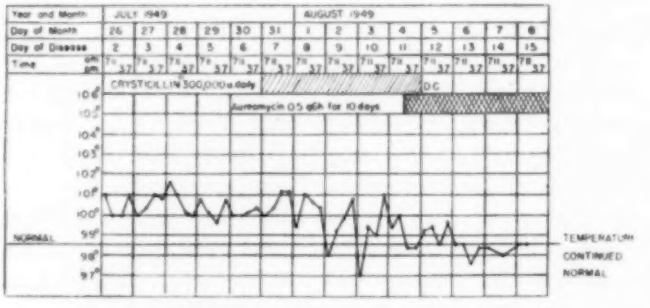


Fig. 3.—Serial electrocardiograms of G. J. D., Case 18.

Laboratory work on admission showed the urine to be loaded with granular and hyalin casts and the blood to have a leukocyte count of 22,950 with 79 neutrophils, 11 lymphocytes and 10 monocytes. The temperature was about 100 F. for three days. An electrocardiogram showed elevated ST segments in all leads. An x-ray of the chest revealed a hazy density at the right lung base and a heart enlarged in all diameters with a water bottle configuration. Treatment consisted of oxygen, plasma, and penicillin. Sputum examinations showed no abnormality. There was

marked improvement by the fifth day, a previously noted gallop rhythm having disappeared, and the cough diminished. The electrocardiogram now showed slight inversion of T-3 and terminal inversion of T-4.

By the 10th day, x-ray of the chest was negative. By the 26th day the electrocardiogram was normal.

CASE 7.—H. H. D., a 20-yr.-old man, was hospitalized on Dec. 25, 1948, complaining of chest pain of a few hours' duration, which he described as a feeling of fullness accentuated by deep breathing. There were slight shortness of breath, made worse by lying down, and paroxysms of coughing productive of small amounts of yellow sputum. There had been moderate sweating at night for three months and a prolonged cold. Examination showed a well-nourished young man in no apparent distress whose only physical abnormalities were an injected pharynx and a pericardial friction rub.

Laboratory studies showed no remarkable findings on admission. Several sputum examinations done the first week were negative. For the first two hospital days there was a temperature of about 99.2 F. An electrocardiogram showed elevated ST segments in leads 1 and 2 and an inverted T in AVF. An x-ray of the chest was normal. The friction rub disappeared after the fourth day and the patient became asymptomatic. By the 19th day the electrocardiogram showed inversion of the T waves in lead 1 and all six chest leads. The sedimentation rate was 10 mm. in one hour on admission and 4 mm. by the 38th day. The tuberculin test was negative, and repeat x-ray examination of the chest, negative. By the 45th day the electrocardiogram was normal.

The major findings of acute pericarditis—i. e., chest pain, pericardial friction rub, electrocardiographic changes and evidence of cardiac enlargement by x-ray—were present in a high percentage of this series (Fig. 1). The chest pain, present in 95%, varied considerably. In cases 15, 16, and 19 it was sudden and severe in onset, simulating coronary occlusion. In most instances it was aggravated by movement, breathing or coughing, and most patients preferred a semiupright position to minimize the pain. Aggravation by swallowing was occasionally noted. As a rule, the pain was dull and constant in the precordium with aggravation by movement or was produced by respiratory or bodily movement. It did not appear to have the "waxing and waning" character noted sometimes in coronary occlusion.[15] In one-half of the cases the pain recurred. In a number of instances this was associated with a febrile response and an exacerbation of the associated pneumonitis.

Electrocardiographic changes indicative of pericarditis [16] were present in all of the cases. Except in one or two instances, six precordial leads as well as the standard limb leads, and often the unipolar limb leads, were obtained. Early changes usually consisted of increased amplitude of the T waves and dome-shaped T waves, in conjunction with ST segment elevation with downward convexity of the elevated ST segment, contrary to the findings characteristic of coronary occlusion.[17] In several cases, the ST segments returned to the isoelectric line, and the tracing appeared practically within normal limits prior to terminal inversion and often frank inversion of the T waves.[18] The T wave inversions in some instances persisted from several weeks to several months. No significant Q waves, ST segment depressions or alterations of the QRS complex or QT interval were noted. No instance of prolongation of the PR interval was found. This is in agreement with the findings of Levy and Patterson [14c] and Nay and Boyer [18] and is considered to be an important point in the differentiation of rheumatic and acute idiopathic pericarditis. In Case 20 there was an episode of paroxysmal auricular flutter. Major arrhythmias have been reported in acute idiopathic pericarditis by others.[19] In many instances the precordial leads reflected the pericarditis much more impressively than did the standard limb leads. In a few of the milder cases diagnosed mainly by serial electrocardiograms, subsequent tracings were ordered solely on the basis of changes in the precordial leads.

A pericardial friction rub that lasted from a few hours to two or three weeks, as in the cases described, was noted in 45% of the cases. In all the severe cases a friction rub was heard.

Enlargement of the cardiac silhouette (demonstrable by x-ray) with a subsequent return to normal occurred in 68% of the cases. There is always a question as to how much of the enlargement is due to cardiac dilatation and how much is due to effusion.[12] Levy and Patterson [14c] found 80% of 25 cases to contain x-ray evidence of cardiac enlargement. Of these, they attributed five to effusion, 16 to dilatation and one to both. In our series the duration of x-ray evidence of cardiac enlargement varied from a few days to seven weeks.

Pneumonitis was present in 64% of the cases, in all but two of which diagnosis was substantiated by x-ray. Of the 13 cases showing x-ray evidence of pneumonitis, there were seven instances of pleural effusion. Generally a leukocytosis (68%) and a shift to the left (68%) were noted. This has been pointed out by other authors.[20]

Fever occurred in all of our cases and was associated with chills in 39%. The fever was usually moderate in degree and lasted from one day to three or four weeks. As in case 12, two or three febrile exacerbations, lasting from a week to 10 days apiece, occasionally characterized the course of the illness. This makes it difficult to evaluate the role of antibiotics and chemotherapy. In at least one-half of these cases, sulfonamides, penicillin, or streptomycin was given and in some instances more than one of the above without definite effect. On occasion, however, the fever disappeared in conjunction with the antibiotic or chemotherapeutic agent, only to recur while the patient was still receiving the drug. We agree with others [21] that there is no response to these drugs. Aureomycin was used in cases 18 and 21. It is questionable whether it had any effect in either case, although in case 18 the patient certainly began to progress within three days following the institution of aureomycin.

CASE 21.—This is an extremely interesting case, as it is quite possible that rheumatoid pericarditis occurred. The patient was a 45-yr.-old white woman who had suffered from rheumatoid arthritis for many years but had been relatively asymptomatic

15. Ethridge, C. B.: Acute Pericarditis Simulating Coronary Thrombosis: Differential Considerations, Hawaii M. J. **5**: 262, 1946.

16. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis: Evolution, Causes and Diagnostic Significance of Patterns in Limb and Chest Leads; Study of 57 Cases, Arch. Int. Med. **61**: 381 (March) 1938. Barnes and Burchell.[15] Vander Veer, J. B., and Norris, R. F.: Electrocardiographic Changes in Acute Pericarditis, J. A. M. A. **113**: 1483 (Oct. 14) 1939.

17. Burchell.[12] Barnes and Burchell.[15] Logue and Wendkos.[14d]

18. Nay, R. M., and Boyer, N. H.: Acute Pericarditis in Young Adults, Am. Heart J. **32**: 222, 1946.

19. Barnes and Burchell.[15]

20. Finkelstein and Klainer.[7] Barnes and Burchell.[15] Logue and Wendkos.[14d]

21. Finkelstein and Klainer.[7] Levy and Patterson.[14c] Logue and Wendkos.[14d]

and fully active for several months prior to her admission in March, 1949, following the onset of sudden, acute chest pain. There were physical, but not x-ray, evidence of pneumonitis, a pericardial friction rub and electrocardiographic evidence of pericarditis. She was discharged on the 23d hospital day completely asymptomatic. There were no joint symptoms during her hospitalization. Three or four weeks later, while on a trip, she experienced a few days of substernal pain. In June, 1949, she had mild arthritic pains and in July, after a period of rather extended and unaccustomed physical exertion, she was admitted with acute severe pleurisy. No pericardial rub was noted on this occasion but there were electrocardiographic changes again compatible with pericarditis. It was on this admission that the patient was given aureomycin after improvement had become manifest. No definite statement as to the role of aureomycin could be made in this case. The clinical course, regardless of its etiology, was essentially the same as in the other cases of this series.

Although the average age in our series was 32, with a range of from 19 to 45, a range comparable with that of 20 to 37 years and an average of 27 for Nay and Boyer's series,[18] the disease can occur at any age, as pointed out by Burchell.[12] Most of the reported cases have been in men (21 out of 22 in this series) but it also occurs in women.[22] As our case material is drawn entirely from a Naval hospital, the sex incidence and age range are probably not representative of the population at large.

COMMENT

In addition to the above series, several patients have been seen in consultation in the past few years, most of whom were referred because of the question of coronary thrombosis or for the evaluation of abnormal electrocardiograms. We are confident that if routine six-chest-lead electrocardiograms were taken of patients with pneumonitis or severe upper respiratory infections, the incidence of this form of pericarditis would be seen to exceed by far all other forms. In 1943 Fuller and Quinlan [14b] reported electrocardiograms taken in 100 cases of upper respiratory infection with fever of over 100 F. In 11 cases there were ST segment elevations of over 2 mm., generally in lead 4, and in five additional cases there were inversions of T-4. On recovery of the patients all electrocardiograms returned to normal. These authors reported one case that was an excellent example of acute idiopathic pericarditis characterized by pneumonitis with successive involvement of all lobes and cardiomegaly. The electrocardiogram had ST elevations in leads 2, 3 and 4 followed by T wave inversions in 1, 2 and 4. All findings returned to normal within five weeks. It was stressed that this patient did not evidence any physical signs of pericarditis.

Seven of our 22 cases were found in March to May of 1948, the discovery largely due to our taking routine electrocardiograms for suspected viral pneumonitis.

The differential diagnosis of acute idiopathic pericarditis concerns mainly acute coronary thrombosis, other types of pericarditis, myocarditis, and other causes of chest pain, such as pleurisy, spontaneous pneumothorax and pulmonary infarction, and, occasionally acute abdominal conditions. The diagnosis must largely be one of exclusion. In the early hours the pain of acute coronary thrombosis may be difficult to differentiate, but important indications of acute idiopathic pericarditis are (1) variation of the pain with movements of the thorax, (2) early presence of the pericardial rub, (3) association with pneumonitis, and (4) absence of reciprocal ST segment depressions. Later, the cardiac enlargement, absence of Q waves or QRS abnormalities, often prolonged fever, and usually rapid return to the normal electrocardiographic pattern are helpful diagnostic signs.

The most frequent pericarditis considered in the differential diagnosis is rheumatic. As shown by Nay and Boyer [18] in a series of pericarditis cases among young adults, which included 25 due to rheumatic fever and 15 of acute idiopathic nature, 100% of the 25 patients with rheumatic fever had preceding or concomitant joint symptoms and nine of them had first or second degree heart block. Neither joint pains nor heart block was found in any of the 15 patients having apparently idiopathic disease. The presence of murmurs, erythema marginatum, rheumatic nodules, and the usually more protracted course may be helpful in the differentiation.

Tuberculous pericarditis may be exceedingly difficult to differentiate, but the effusion is characteristically slow in development and massive in quantity, is often associated with dependent edema and ascites, and persists for a relatively long period.[23] In our experience the patient with this condition was more toxic, the course much more severe, and the infection generally fatal. Also, there was usually other evidence of tuberculosis, or else it subsequently developed.

Pericarditis associated with rheumatoid arthritis offers a difficult differential diagnosis, as seen in case 21. The incidence of rheumatoid pericarditis as reported by Graef and his colleagues,[8] is striking. They found evidence of pericarditis, usually old adhesive or obliterative lesions, in one-half of 66 necropsies of rheumatoid arthritics. In four cases they noted clinically unsuspected acute fibrinous pericarditis. This compares with 19 cases of pericarditis (nine associated with endocarditis) out of 38 autopsied patients with rheumatoid arthritis reported by Young and Schwedel.[24] Joint symptoms may be absent in a rheumatoid patient with acute pericarditis as they were in our case 21 and as noted in Granirer's case.[25]

Idiopathic myocarditis, which is beginning to be recognized with apparently increasing frequency, also confuses the diagnosis. Exactly where idiopathic pericarditis stops and myocarditis begins, and whether they may be due to the same agent or agents are not known. In our experience, idiopathic myocarditis has been highly fatal although sometimes with a moderately protracted course. The presence of gallop rhythm, progressive fall in blood pressure, pulsus alternans, cardiac failure and hepatomegaly are often useful distinguishing features. The question of whether cardiac enlargement is due to effusion or dilatation, or both, is not always important in pericarditis (although Wolff [26] has pointed out that dilatation usually does not occur in tuberculous or suppurative pericarditis) but as in distinguishing it from myocarditis, it may be of prognostic value. We have found that angiocardiog-

22. Burchell,[12] Nay and Boyer.[18]

23. Smalley and Ruddock,[167] Stepman, T. R., and Owyeng, E.: Clinically Primary Tuberculous Pericarditis, Ann. Int. Med. **27**: 914, 1947.

24. Young, D., and Schwedel, J. B.: Heart in Rheumatoid Arthritis: Study of 38 Autopsy Cases, Am. Heart J. **28**: 1, 1944.

25. Granirer, L. W.: Pericardial Effusion in Rheumatoid Arthritis, M. Clin. North America **30**: 562, 1940.

26. Wolff, L.: Acute Pericarditis with Special Reference to Changes in Heart Size, New England J. Med. **229**: 423, 1943.

raphy is a satisfactory method of determining this question. This procedure has been advocated by Williams and Steinberg.[27] Unless the patient actually has heart failure, the danger of angiocardiography is not great.

In addition to the usual procedures for the establishment of an etiological diagnosis of the pericarditis, including a search for foci of infection, blood cultures, complement fixation tests for amebiasis and lymphopathia venereum, tuberculin tests, and agglutinations for Bacterium tularense, other special tests should not be overlooked. Unless the course has been extremely severe and the effusion rather marked and protracted, we have seldom considered pericardial paracentesis for the determination as to whether there is or is not a pericardial effusion or as to its degree. When the usual means have failed, we generally prefer angiocardiography to paracentesis. Electrokymography can also be of aid in some instances with this problem. However, if tuberculous pericarditis is strongly suspected and effusion has been demonstrated, paracentesis should be done in order to obtain a specimen for bacteriological diagnosis prior to the administration of streptomycin.

Until recently, the treatment of acute idiopathic pericarditis was entirely symptomatic. Taubenhaus and Brams [14b] have reported three cases with relief of symptoms and decrease in fever and pulse rate 24 to 48 hr. after starting aureomycin therapy. However, owing to the variability of the disease more data on this treatment will be required before its proper role can be determined.

In every case of acute idiopathic pericarditis a point is reached at which the decision as to ambulation and discharge from the hospital must be made. It is our opinion that the electrocardiogram has little short-term prognostic value in deciding this point, and the decision rests on the over-all clinical picture of the patient. If the patient has been afebrile and asymptomatic for a few days and has reasonable vigor in consideration of the length and severity of his illness, he is allowed to become ambulatory and is discharged a few days later. He is, however, cautioned as to the possibility of a relapse and is advised to restrict his physical activity moderately for a period of several weeks. Fortunately, when early relapse has occurred, it has been mild. The four recurrences in Levy and Patterson's series were also mild.[14c]

The etiology of acute idiopathic pericarditis and primary atypical pneumonia remains undetermined, but their close association, as seen in this series strongly suggests the same cause. It may be that the pericardium is involved by direct spread of the infectious agent from the adjacent lungs and pleura. However, we often conjecture that so-called virus pneumonia is a manifestation of a generalized disease affecting many or all organs, and that it often finds expression in a serositis. Hence, pleurisy and pericarditis, and possibly peritoneal inflammation, are probably more commonly associated with virus pneumonitis than is generally recognized. We often wonder whether there is not a related "benign peritonitis" associated with pneumonitis and upper respiratory infections, which might account for some of the pathological reports of "surgical appendix." Usually the surgeon hesitates to operate in the presence of an obvious respiratory infection, but it may be, as suspected in some cases of acute idiopathic pericarditis, that the respiratory tract infection is latent and thus the association is not apparent. Certainly we feel that we have seen occasional cases of peritoneal-like pain associated with upper respiratory infections, which are not easily explained on a referred basis, as that in lobar pneumonia, for instance.

It is also possible that a peritoneal serositis might occur not only from a hematogenous spread of the infectious agent but might gain access from the pleural cavity in the manner postulated for Meigs' syndrome. In any event it is quite possible that, if searched for, instances of peritoneal serositis can be found associated with relatively benign infections of the respiratory tract, pleura and pericardium.

SUMMARY

Twenty-two cases of acute idiopathic pericarditis, of which one possibly is an example of rheumatoid pericarditis, have been presented together with a review of the literature on this subject.

The main clinical point to be remembered is the development of substernal chest pain, aggravated by movement, in a patient with an apparently benign respiratory infection. A pericardial rub, cardiomegaly detectable by x-ray, and the typical electrocardiographic findings complete the picture of acute pericarditis. The diagnosis of acute idiopathic pericarditis is then established by the exclusion of the specific forms of pericarditis and the benign, but often relapsing, course.

The major and minor findings associated with the disease have been tabulated on a percentage basis. The differential diagnosis has been discussed and the role of angiocardiography in aiding in the differentiation of cardiac dilatation and pericardial effusion has been stressed. The purpose of this paper has been to aid in establishing in detail the natural course of this disease, not only for a more widespread diagnosis, but also for the proper evaluation of antibiotic therapy, such as aureomycin, chloramphenicol (chloromycetin®), and terramycin.

United States Naval Hospital.

27. Williams, R. G., and Steinberg, I.: Value of Angiocardiography in Establishing Diagnosis of Pericarditis with Effusion, Am. J. Roentgenol. 61: 41, 1949.

The Physician and His Workshop.—Perhaps the best observers of the human mind in its working are good general practitioners, who, gaining the respect and confidence of their patients, passing freely into and out of their homes and knowing intimately their social and economic conditions, are able to observe over many years the reactions of mind and body to anxiety. Were this study their only function, they would not be good psychologists, but as their primary duty is the diagnosis and relief of physical illness, they can sift their observations with a shrewdness and judgment not always given to the specialist. Theoretical and experimental psychology, as taught in the universities, has its place in the study of the human mind, but is limited because it is largely based on hypothesis and tests performed in an unnatural environment. Who can strip the curtain from the soul in lecture hall or laboratory? The mind of man, which ranges beyond the flaming ramparts of the world, eluded Lucretius and eludes us all. But by the bedside or in the consulting room it is given to us to lower the barriers and to gaze with awe on some of the arcana of the mind.—C. G. McDonald, The Physician and His Workshop, *The Medical Journal of Australia*, June 23, 1951.

NOCTURIA IN THE AGED

Seymour W. Rubin, M.D.
and
Henry Nagel, M.D., Baltimore

Nocturia is a frequent complaint and an important symptom of the aged. The lack of sleep, restlessness, anxiety, and exhaustion caused by nocturia have been responsible for many an irritable household; and, far more important to the individual, these are frequently the cause of chronic cardiac failure.

Nocturia is a symptom that occurs in the vast majority of aged persons. We have studied the cause of this symptom in 144 patients with particular emphasis as to age, sex, blood pressure, blood urea, and urine analysis.

In a general way the urologist and the internist approach the problem of nocturia from different viewpoints. The urologist defines nocturia as a frequency of urination at night without reference to the amount of urine produced. The internist thinks of nocturia as a nocturnal frequency resulting from an excessive amount of urine produced. However, both groups must not lose sight of the fact that nocturia is very often the first subjective symptom of frequency and often of urgency. For example, if one has to urinate every three hours, there might be two nocturnal occurrences, though during the day such frequency might not be disturbing—certainly not enough to urge a patient to seek medical advice.

There are several causes of nocturia, conveniently classified as (1) physiological, (2) psychological, (3) cardiac, (4) renal, and (5) obstructive or urological.

The physiological cause is most evident after one drinks a large amount of liquid.

The psychological cause of nocturia has received little treatment in either textbooks or current literature. The sleep of the older person is not so sound as that of the younger one. When the aged person awakens in the middle of the night and cannot fall asleep right away, he then finds it convenient to urinate though there may not be any real urgency—not unlike the younger person getting a sandwich when sleeplessness is bothersome. One can also easily acquire the habit of getting up at night to urinate even though sleep is easily enjoined. Such habits are often acquired and carried over from past illnesses. This is particularly so in older men who have suffered long from vesical neck obstruction and have delayed proper and adequate therapy for years. This readily acquired habit of a previous long-standing organic lesion is only too frequently seen in geriatrics and will be discussed later in this paper. Frequency of emotional origin is familiar to us all, especially to those who have taken American Board examinations.

A third cause is cardiac failure. A healthy person secretes more urine per hour during activity than during sleep because more fluid is ingested during the day, and, when the heart is functioning properly, no retention of fluid in the tissues will occur. Moreover, there is a slight physiological fall of blood pressure during the night, which lowers the filtration pressure in the kidney. In the patient with cardiac disease, however, as one of the first signs of decompensation, there is a nocturia which consists in the elimination of the manifest or subclinical edema fluid. Because of the recumbent position during the night, the venous pressure, and therefore the capillary pressure, in the lower extremities becomes diminished. These facts help to reverse the process of edema formation and thus lead to reabsorption of the edema fluid into the blood stream, with its excretion as urine and consequent nocturia. It has also been asserted that the kidneys themselves work better in the horizontal position, either beeause of better venous return from the kidneys or because of other factors, perhaps similar to the ones that play a role in orthostatic albuminuria.

A fourth cause for nocturia is renal failure. In such cases the kidneys are unable to concentrate the urine, and, in order to get rid of the waste products of metabolism in the presence of a low specific gravity, the normal diurnal variation in urine formation is modified by a more continuous flow of urine of a larger volume and at a more uniform rate throughout the day and night. This results in nocturnal frequency. Normally about 30 Gm. of urea is excreted daily in a concentration of about 2 per cent, with a specific gravity of 1.020 and a consequent volume of 1,500 cc. In cases of renal failure, the kidneys cannot concentrate the urine and a fixed specific gravity of 1.010 may be seen. In such cases, the daily excretion of 30 Gm. of urea at a concentration of 1 to 1.25 per cent would require the excretion of 3,000 cc. of urine spread fairly evenly over the 24 hours.

The fifth group of causes for nocturia, and by far the most important and most serious, is the urological—the result of some pathological condition in the urinary tract and, most frequently, the end parts of that tract. The urological causes can be divided into four groups; namely, infective, reflex, diminished bladder capacity, and obstructive.

Infection of either the upper or the midportion of the urinary tract frequently results in urgency or frequency and is a common presenting symptom along with the other findings of urinary tract infection.

Reflex nocturnal and diurnal frequency is readily recognized in persons suffering from calculi in the urinary tract. It is very often complained of during the attack of renal colic, although urination itself may be ineffectual. The reflex frequency of an emotional nature has been suggested in the paragraph on psychological causes. Pathological disease of structures surrounding the kidney may also cause nocturia by irritation.

Diminished bladder capacity results in frequency and nocturia and is especially complained of in patients with Hunner's ulcer, the contracted bladder of tuberculosis or the spastic, tender bladder of neoplasm, cystitis and calculous disease.

The obstructive lesions are the most serious causes of nocturia. In the male they are due to benign prostatic hyperplasia and in the female to a cystocele. The obstruc-

From the Urological and Medical Departments of the Levindale Hebrew Home and Infirmary; visiting urologist (Dr. Rubin) and resident physician (Dr. Nagel).

tive lesions can be placed into four groups: (1) bladder neck contractions—e. g., median bars, fibrosis, hypertrophied interureteric bars; (2) prostatic enlargements, either benign or malignant (the size of the gland is of little importance), and postprostatectomy conditions with persistent nocturia; (3) bladder calculi, cystocele, diverticuli, etc., with obstruction to the free outflow of the bladder urine, and (4) urethral obstruction, e. g., strictures.

An additional comment about the postoperative prostatic cases is pertinent. We have observed in many aged men the persistence of nocturia following prostatectomies and resections. The frequency of nocturia after prostatic surgery is noticeably less, and the stream is freer. Two points of great importance need to be emphasized in these postprostatectomy patients: the back pressure that has been transmitted to the kidneys, with its associated chronic uremia, and the strain to the heart with its associated chronic heart failure are no longer evident. These patients are still alive as a result of the relief of these factors. The latter point, however, needs additional emphasis because of its neglect in the literature and the reluctance of the internist to accept the obstructive prostate as the cause of many cases of chronic heart failure (from exhaustion). These patients look very bad and are very poor risks. Nevertheless, in order that these men may live, prostatectomy must be performed. The exhaustion, edema and breathlessness will disappear with the relief of the obstruction to the free outflow of urine.

One other point can also be made from our observations of these aged men: Those who had a longer history of frequency prior to prostatectomy had severer and more persistent nocturia, and those who were subjected to prostatectomies shortly after the onset of the symptoms had few or no residual urinary complaints. It is probably the development of chronic cystitis with hypertrophy and fibrosis of the bladder wall in these long-standing cases that persists as the cause of nocturia after the removal of the obstructing prostate.

We have also observed that the symptoms of nocturia have persisted longer after transurethral prostatic resection than after open prostatic surgery. This, too, can be attributed to the persistent pyuria observed after resections and to the presence of slough leading to local fibrosis and scarring.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is rather simple. The urological cases are screened by physical examination, urinalysis and cystoscopy. The origin of the nocturia, cardiac or renal, must then be determined. In the former case, the specific gravity of the urine will be normal or high. In the latter case, it will be lower, for reasons explained above. Likewise, in the renal cases, there will be polyuria during the day, too, while in the cardiac cases the output during the day is relatively small. In most cases of renal insufficiency, at least in the earlier stages, there is an increased 24-hour output as compared with the output of a cardiac patient. Finally, energetic cardiac therapy in an early decompensated cardiac patient will be followed by prompt improvement in the urinary findings and also in the nocturia itself.

In our studies we have tried to correlate the degree of nocturia with the various factors mentioned above. However, without presenting a large volume of statistics, we should like to point out that we found a slight but definite increase in the degree of nocturia among men over that among women. This fact seems undoubtedly to be due to obstruction from the hypertrophied prostate.

We also found that the average blood urea of those patients who suffered more from nocturia was not higher than the urea of those who suffered from a lesser degree of nocturia. This fact, generally said, means that renal failure is not a major cause of nocturia in aged persons, though it is conceded that the blood urea is not a very accurate yardstick of kidney function. Also, the fact that the specific gravity of the nightly specimen of urine of the patients with a higher degree of nocturia was normal opposes renal failure as the cause of their nocturia.

There was no clearcut relationship between the blood pressure and the nightly frequency, though the tendency was for those patients with a systolic blood pressure of 165 to 200 to have a higher degree of nocturia than those with blood pressures below 150 or above 200 systolic (millimeters of mercury).

The degree of nocturia was highest in the age group between 70 and 80. The younger ones and those who were more than 80 showed a lesser degree of nocturia. To paraphrase the obvious remark once made by a famous pathologist, "A person who lives to be 90 must have chosen a very good cardiovascular system."

SUMMARY

The causes of nocturia in the aged may conveniently be divided into physiological, psychological, cardiac, renal, and urological.

The urological causes are the most important, and the diagnosis can be readily established. The etiological factors are infective, reflex, diminished bladder capacity, and obstructive. The last group includes bladder neck contractions, prostatic enlargements, bladder calculi, diverticula and cystoceles, and urethral obstructions.

It has also been our observation in prostatectomy patients that the longer the symptoms have been present prior to prostatectomy the longer and more bothersome the persisting symptoms were after prostatectomy. Generally, nocturia persisted longer after transurethral resection than after open prostatic surgery.

Though the urological causes of nocturia are the most important, in our opinion the main cause of nightly frequency is subclinical or manifest cardiac decompensation.

1701 Eutaw Place (17) (Dr. Rubin).

Practical Psychotherapy.—Allowing the patient to talk of his fears and other problems is called ventilation. This is a valuable therapeutic tool if the physician accepts the patient's story with an understanding non-condemning attitude. One should not force the patient to reveal material that is obviously very upsetting. . . . Be cautious of the patient who divulges a great deal of highly personal and bizarre material at his first visit to you. Such a patient may be near a psychotic break. Do not be distressed if the patient cries during the interview; usually he feels better for it.—Robert H. Crede, M.D., Applied Psychosomatic Medicine in General Practice, *Annals of Western Medicine and Surgery*, August, 1951.

LIGATION OF INTERNAL CAROTID ARTERY FOR ANEURYSMAL LESIONS OF CIRCLE OF WILLIS

Robert C. Bassett, M.D., Ann Arbor, Mich.
and
H. Harvey Gass, M.D., Detroit

The management of aneurysms of the circle of Willis is a trying problem. The practitioner faced with the care of a patient with such a lesion, whether it is ruptured or unruptured, finds little peace of mind in the decision to follow a conservative program in the hope that the natural reparative processes will somehow produce a cure. The knowledge that this happens only infrequently makes the responsibility of that decision even more burdensome.

The diagnosis of aneurysm of the circle of Willis is being made more frequently as there is greater recognition that most subarachnoid hemorrhages are caused by rupture of such a lesion. Even though he may eventually discharge from the hospital about one-half of his patients with bleeding aneurysms, the practitioner finds little comfort in the thought that such patients, who are frequently young, are in constant jeopardy. At any moment, without warning, bleeding may start again. The patient with an unruptured aneurysm presenting only neighborhood symptoms is in a similar precarious predicament.

Ultimately most of these patients will die of subarachnoid or intracerebral hemorrhage. Until recent years, however, the practitioner had no recourse other than to provide the patient with supportive treatment and nursing care.

Since the first efforts at neurosurgical treatment by Dott,[1] Tonnis,[2] and Jefferson [3] less than two decades ago and the more recent stimulus of Dandy's [4] monograph, the number of surgical conquests of these lesions has been increasing steadily. The risk involved in such surgery remains great. Neurosurgeons consider direct intracranial attack on these lesions the most hazardous surgical experience encountered, and some prefer to avoid it. Despite this, surgical knowledge is accumulating gradually. The degree of risk associated with surgery in different locations and types of aneurysms is becoming clarified, and specific surgical techniques are evolving. The purpose of this report is to present the results of experience at the University of Michigan Hospital with simple ligation of the internal carotid artery in the neck as treatment of aneurysms of the circle of Willis.

From the Department of Surgery, University of Michigan Medical School and Hospital (Dr. Bassett).

1. Dott, N. M.: Intractanial Aneurysms: Cerebral Arterioradiography; Surgical Treatment, Tr. Med.-Chir. Soc. Edinburgh, 1932-1933, in Edinburgh M. J. **40**: 219 (Dec.) 1933.
2. Tonnis, W.: Erfolgreiche Behandlung eines Aneurysma der Art. commun. art. cerebri, Zentralbl. Neurochir. **1**: 39, 1936.
3. Jefferson, G.: On the Saccular Aneurysms of the Internal Carotid Artery in the Cavernous Sinus, Brit. J. Surg. **26**: 267, 1938.
4. Dandy, W. E.: Intracranial Arterial Aneurysms, Ithaca, N. Y., Comstock Publishing Company, 1944.
5. Sweet, W. H., and Bennett, H. S.: Changes in Internal Carotid Pressure During Carotid and Jugular Occlusion and Their Clinical Significance, J. Neurosurg. **5**: 178, 1948.
6. Schorstein, J.: Carotid Ligation in Saccular Intracranial Aneurysms, Brit. J. Surg. **28**: 50, 1940.
7. Olivecrona, H.: Ligature of the Carotid Artery in Intracranial Aneurysms, Acta chir. scandinav. **91**: 353, 1944.

Not infrequently, the internal carotid artery is ligated in the neck as one part of the "trapping" procedure by which an aneurysm of the circle of Willis may be cured. In this procedure the aneurysm is trapped by interrupting the blood supply to it by ligation of the internal carotid artery proximally in the neck and clipping that artery distal to the aneurysm intracranially. In this report we are concerned only with the therapeutic effect of occluding the internal carotid artery in the neck.

Sweet and Bennett,[5] by making direct measurements of the change in blood pressure in the internal carotid artery in the neck distal to the point of occlusion, showed that intracarotid pressure falls approximately 50% at the point of measurement. They reasoned that such a reduction in pressure should be beneficial in the treatment of intracranial aneurysms of the internal carotid artery. Our previous clinical observations also suggested that ligation of the internal carotid artery in the neck was a gratifying procedure at times. We therefore reviewed the records of patients treated in this way to evaluate the usefulness and safety of the procedure in routine management of these lesions.

Reports in the literature deal with the safety of the procedure but little information is given regarding therapeutic benefit. In 1940 Schorstein [6] reported 60 cases (27 collected from the literature and the remainder from British neurologists and neurosurgeons) in which the internal carotid artery was ligated for a saccular aneurysm of the circle of Willis. He concluded that internal carotid ligation was a uniformly benign procedure with infraclinoid aneurysms. Preoperative impairment of the cerebral circulation by hemorrhage or compression of basal arteries by the aneurysm favored the development of postoperative cerebral complications or death, a situation most likely to occur with supraclinoid aneurysms. Among the 60 patients, there were eight deaths resulting from operations and eight patients in whom neurological complications developed. Dandy [4] stated in his monograph that in only one of the 36 cases in which the internal carotid artery was ligated in the neck was the procedure not tolerated, with the development of a late fatal cerebral complication. No definite information is revealed in these two reports regarding the efficacy of this procedure as the only measure in the treatment of aneurysms.

As a result of his experience with 24 patients in whom the internal carotid artery was ligated, Olivecrona [7] felt that the procedure was safe for those with infraclinoid aneurysms, somewhat less safe for those with supraclinoid aneurysms, and generally unsafe in arteriovenous fistulas, whether they were supra- or infraclinoidal. Again no specific information was available regarding the efficacy of the procedure so far as the effect on the aneurysm itself is concerned.

Poppen [8] reported that in more than 100 ligations of the carotid system permanent partial hemiplegias occurred on the contralateral side in four patients, but three of these patients were not prevented from carrying out their usual activities. He stressed the importance of proper technique in ligation, constant perfusion of the superior cervical ganglion with procaine via a polyethylene tube for two or three days, and the use of heparin postoperatively in patients who had not had a subarachnoid hemorrhage within three weeks of the ligation as an effort to reduce late complications, especially complications resulting from late thrombosis or embolism. In his report, however, definite information regarding the therapeutic value of this procedure was also lacking.

TABLE 1.—*Saccular Aneurysms*

Patient	Sex	Age, Yr.	Duration of Follow-Up	History of Subarachnoid Hemorrhage Prior to Ligation	Hemorrhage After Ligation	Improvement		Tolerance to Ligation
						Symptomatic	Objective	
S. K.	F	47	1 mo.	No	No	Yes (pain)	Yes (ocular palsy)	Uneventful
C. M.	F	40	7 mo.	Yes	No	Yes (pain)	Yes (ocular palsy)	Uneventful
M. M.	F	46	2 mo.	No	No	Yes (pain, bruit, and diplopia)	Yes (ptosis and ocular palsy)	Uneventful
V. A.	F	41	9 mo.	No	No	Yes (pain and diplopia)	Yes (ptosis and ocular palsy)	Uneventful
J. P.	M	41	9 mo.	Yes	No	Yes (pain and diplopia)	Yes (ptosis and ocular palsy)	Uneventful
E. A.	F	55	7 mo.	Yes	No	Yes (pain and diplopia)	Yes (ptosis and ocular palsy)	Recovery from initial aphasia and hemiplegia by removal of clip and stellate ganglion block; tolerated after preliminary partial occlusion and cervical sympathectomy
B. H.	F	32	9 yr.	No	No	Yes (pain and bruit)	Yes (ocular palsy)	Uneventful
A. F.	M	58	11 mo.	Yes	Yes (death 11 mo. later)	No (large, thin-walled aneurysm)	.....	Uneventful
G. B.	F	62	4 days	No	No	.....	.....	Coma during occlusion and death in 4 days
A. S.	F	41	2 days (trapping)	No	No	Yes	Yes (ptosis)	Transient hemiparesis during compression in operating room lasting 10 minutes
M. Q.	F (pregnant)	23	2 mo.	Yes	No	.....	.....	Transient hemiparesis 1 day later; complete recovery
H. C.	F	18	2 days (trapping)	No	No	No	.....	Uneventful
L. F.	M	19	3 mo.	Yes	Yes (death 3 mo. later)	Yes (pain)	No (large aneurysm)	Uneventful
K. W.	M	41	7 mo.	Yes	No	.....	.....	Preexisting left hemiparesis made worse by ligation but recovered to previous state 7 mo. later
K. K.	M	33	5 days (trapping)	Yes	?	.....	.....	Hemiparesis 3 days after ligation
H. B.	F	22	8 days (trapping)	No	No	Yes (bruit)	No	Transient hemiparesis and aphasia with full recovery
L. H.	F	38	1 mo.	Yes	No	.....	Yes (ptosis)	Slight hemiparesis and hemisensory syndrome 10 days following ligation, with subsequent recovery
Total, 17				Yes — 9 No — 8	Yes — 2 No — 15	Yes — 10 No — 2	Yes — 9 No — 2	Tolerated with no or negligible permanent deficit—15 Death due to ligation—1

SACCULAR ANEURYSMS

Table 1 tabulates the course of 17 patients with saccular aneurysms of the circle of Willis proved by arteriography and/or direct surgical visualization who were treated by ligation of the internal carotid artery in the neck.

Ligation was the only form of surgical treatment used for 10 of these patients. In three of them craniotomies were also performed, but no direct definitive treatments were carried out and the surgical procedures consisted of establishing the diagnosis by direct visualization and needling. In the remaining four patients a trapping procedure was done, but there were intervals of two to eight days between the ligations and craniotomies during which the effects of the ligations alone upon neighborhood symptoms could be observed.

A permanent ligation was not performed unless the patient under local anesthesia was able to tolerate occlusion on the operating table for at least 30 minutes and usually one hour without development of additional neurological symptoms. This tolerance test on the operating table should exclude the cases in which adequate collateral circulation to the homolateral hemisphere is not available because of anomalies of the circle of Willis. Sweet [5] has demonstrated by direct internal carotid artery pressure measurements that the Matas procedure (digital compression of the internal carotid artery in the neck) cannot completely occlude the artery and is there-

8. Poppen, J. L.: Ligation of the Internal Carotid Artery in the Neck: Prevention of Certain Complications, J. Neurosurg. 7: 532, 1950.

fore not reliable. In no instance in our series was the artery transected.

On admission, 14 of the 17 patients presented symptoms or signs other than those of subarachnoid hemorrhage, including various combinations of the following: ptosis, diplopia, ocular palsy, bruit, proptosis, facial paresthesias, and ocular or head pain not associated with recent subarachnoid hemorrhage. Five of these 14 patients had such symptoms in addition to recent subarachnoid hemorrhages. Amelioration of these symptoms or signs following ligation of the internal carotid artery is an indication of the efficacy of the treatment. In other words, when improvement in these symptoms or signs occurred it was probably due to shrinkage of the aneurysm, with resultant decrease of pressure on neighborhood structures.

Eleven of these 14 patients showed such improvement in local symptoms or signs following ligation. In eight of these the improvement was noticeable immediately or within two weeks after ligation. Thus in several of these patients ptosed eyes began to open or ocular palsies began to improve within a few days after ligation or pain

TABLE 2.—*Carotid-Cavernous Sinus Fistulas*

Patient	Sex and Age, Yr.	Duration of Follow-Up	Improvement		Tolerance to Ligation
			Symptomatic	Objective	
B. B.	F 58	2 mo.	Yes (bruit)	.....	Uneventful
B. C.	F 44	6 days	Yes (bruit)	.....	Uneventful
C. T.	M 45	7 mo.	Yes (bruit)	None (exophthalmos persisted)	Uneventful
R. D.	F 57	4 mo.	Yes (bruit)	None (exophthalmos persisted)	Uneventful
P. O.	M 17	3 yr.	Yes (bruit)	Yes (exophthalmos)	Uneventful
Total 5			5	1	5

was relieved immediately. For three of the patients there is no mention in their records of when improvement first began, but at one month, four months, and nine years postoperatively such improvement is recorded. In eight of the 11 patients the improvement was maintained or increased at one month, six weeks, two months, six months, seven months, seven months, eight months, and nine years following ligation, when these patients were last heard from. Four were completely or almost completely recovered. In two of these 11 improved patients craniotomy was done for trapping two and eight days after cervical carotid artery ligation, and so a longer follow-up on the effect of ligation alone is not possible. The remaining patient, who had an unusually large aneurysm with initial improvement of headache and trigeminal pain following carotid artery ligation, died suddenly at home three months later, presumably of subarachnoid hemorrhage.

Of the three other patients with local signs and symptoms who did not improve, one experienced no relief with carotid artery ligation from her head pain which was her only symptom and intracranial trapping was performed two days later. Another patient, 62 years of age, became semicomatose after 20 minutes of partial occlusion on the operating table and died four days later. The third patient, who entered with a subarachnoid hemorrhage, had a large thin-walled aneurysm, but obtained no relief from his pain by carotid artery ligation; he died one year later at home, presumably from a ruptured aneurysm.

There were three patients who presented no local signs and symptoms upon admission. Two of these manifested only subarachnoid hemorrhages. One had had no further bleeding seven months after cervical carotid artery ligation. The other, whose condition was critical upon admission, had failed to improve five days after ligation, at which time an intracranial trapping was done. The third patient had had a previous subarachnoid hemorrhage at the seventh month of pregnancy. Ligation was done as a prophylactic measure during the fourth month of a second pregnancy. She was subsequently delivered by cesarean section at term.

Of these 17 patients, nine showed no additional symptoms resulting from ligation of the internal carotid artery. In four patients transient hemiparesis or aphasia developed which responded promptly to treatment so that total permanent ligation was ultimately tolerated without additional neurological deficit. In one of the remaining four patients a preexisting left hemiparesis was made worse but seven months postoperatively recovery to the original degree of hemiparesis had occurred. In another a mild left hemiparesis and left hemisensory syndrome developed 10 days postoperatively but was scarcely present six weeks postoperatively. In a third patient hemiparesis developed three days postoperatively, and a trapping procedure was done two days later. The fourth patient, already mentioned, died as a result of partial occlusion of the internal carotid artery. Thus, in this group of 17 patients with saccular aneurysms of the circle of Willis, 15 patients tolerated the procedure with little or no serious permanent difficulty.

CAROTID-CAVERNOUS SINUS ANEURYSMS

There were five patients who underwent ligation of the internal carotid artery in the neck for carotid-cavernous sinus aneurysms (Table 2). The diagnosis was based on the presence of a unilateral pulsating exophthalmos with bruit. Trauma preceded the appearance of symptoms in three patients. In two cases arteriography demonstrated carotid-cavernous sinus fistulas.

In each case improvement followed ligation of the internal carotid artery in the neck. In all patients the bruit was strikingly reduced, disappearing entirely in two patients. The exophthalmos was significantly reduced in one patient. This improvement was present six days, two months, four months, seven months, and three years after ligation when these patients were last heard from.

The ligation was tolerated perfectly in all five patients, with no additional symptoms resulting from the procedure.

In none of the 22 patients who underwent ligation did subsequent complication develop at the site of ligation.

COMMENT

Eleven out of 17 patients with saccular aneurysms and all five patients with carotid-cavernous sinus aneurysms who underwent ligation of the internal carotid artery in the neck showed significant improvement in local neighborhood signs and symptoms caused by the aneurysms. Two other patients, who showed no such signs or symptoms but who had previously had subarachnoid hemor-

rhages, had not had further bleeding or symptoms seven months and six months later.

One patient, aged 62, died as a result of the operation. Serious permanent neurological deficit attributable to ligation did not otherwise occur except possibly in one patient with a recent subarachnoid hemorrhage, in whom hemiparesis developed three days following ligation. The outcome of this hemiparesis is not known, since he underwent intracranial trapping two days later. It is also possible that this hemiparesis might have been due to recurrent bleeding rather than to ligation in this patient.

The risk involved in ligation of the internal carotid artery in the neck is undoubtedly greater in elderly people. Two of the eight patients who showed transient or permanent ill effects from ligation were over 50 years of age—55 and 62. (Four patients not included in this series are known to us who suffered ill effects from ligation or manipulation of the internal carotid artery in preparation for ligation for other reasons; all these patients were over 50 years of age—56, 54, 55, and 71.) Only one patient (aged 58) over 50 years old tolerated internal carotid artery ligation uneventfully.

In some respects this is a selected group of cases from the standpoint of typical cases with saccular aneurysms of the circle of Willis. The percentage of patients with unruptured aneurysms upon admission (47%) is probably higher than in an average urban hospital, since the clinical condition of patients with ruptured aneurysms and subarachnoid or intracerebral hemorrhage would not permit their being referred to the University Hospital with the same ease as ambulatory patients. In the latter group the aneurysms are manifested largely by local symptoms and signs. Such presenting neighborhood symptoms indicate a certain anatomical location of the aneurysm, since it must, unless very large, exist in a precise area to press upon the third, fourth, fifth, or sixth cranial nerves. It is this pressure which accounts for most of the presenting neighborhood signs and symptoms (ptosis, diplopia, ocular palsy, ocular and head pain, and paresthesias). The third, fourth, fifth, and sixth nerves lie below the level of the clinoid processes. The bifurcation of the internal carotid artery into the middle and anterior cerebral arteries occurs above the level of the clinoid processes. Aneurysms of the circle of Willis, therefore, which take their origin from the middle cerebral, anterior cerebral, or anterior communicating artery are more likely to be supraclinoid. There are few anatomical structures other than optic pathways above the level of the clinoid processes which a supraclinoid aneurysm, unless large, would affect by direct pressure. Minor visual field changes from pressure against optic nerves, chiasms, or tracts are less likely to be detected than loss of function of oculomotor nerves. Consequently, the likelihood of unruptured supraclinoid aneurysms producing symptoms which will be recognized readily and traced to their cause is considerably less than with unruptured infraclinoid aneurysms.

The group of saccular aneurysms reported here is probably weighted in favor of infraclinoid aneurysms or those of the intracranial portion of the internal carotid artery (or of the posterior communicating artery, statistically less common). Corroboration of this deduction by fact is not possible in this series since the exact origin of the aneurysms cannot be determined reliably by arteriograms. It must be assumed, therefore, that this group of aneurysms for the most part originates below the bifurcation of the internal carotid artery (and what surgical and arteriographic verification there is supports this contention), being fed in large part from the internal carotid artery. It would seem that removal of this direct pressure would have its maximum effect in permitting shrinkage of aneurysms which come off the main trunk of the artery; the least effect, if any, would be on aneurysms coming off one of the supraclinoid tributaries (middle cerebral, anterior cerebral, anterior communicating arteries) which would be maintained by circle of Willis collateral circulation in an adequate system.

The improvements already noted may be presumed to have occurred for the most part in patients with infraclinoid aneurysms, particularly in those whose conditions were not complicated by the additional damage incident to rupture and hemorrhage. The tendency for recurrent subarachnoid hemorrhage to develop in the third week after the initial bleeding, which may be concerned with softening of the clot at the site of perforation, and Schorstein's observation that tolerance to ligation is poorer when preoperative hemorrhage has occurred suggest that internal carotid artery ligation alone may not be worth-while treatment if recent subarachnoid hemorrhage has occurred. Resort to intracranial trapping or clipping may then be considered. It is unlikely that most unruptured, supraclinoid aneurysms can be recognized readily in office practice, and, even if they could be, it is doubtful that internal carotid artery ligation would have an equivalent thrombosing effect upon them.

The high incidence of early symptomatic improvement in these cases therefore suggests that ligating the internal carotid artery in infraclinoid aneurysms may be beneficial, particularly for unruptured aneurysms, and especially in patients under the age of 50 when the risk of serious permanent damage is small.

The follow-up on many of these patients is admittedly short; hence no conclusion can be drawn from these cases regarding the effect on life expectancy or recurrence rate. Ligation of the internal carotid artery alone, however, does not carry with it the additional hazard, emotional trauma, and strain associated with a direct surgical intracranial attack. Such an intracranial approach could be done subsequently if it is indicated by further difficulty and might then be even less hazardous. In view of the helplessness of the physician called upon to deal with these treacherous lesions, ligation of the internal carotid artery in the neck in the conditions specified appears to be of practical value and deserving of clinical application.

Definite improvement without intolerance followed this procedure when performed for carotid-cavernous sinus aneurysms in this series, although other reports have been less favorable regarding tolerance of carotid artery ligation in this type of lesion.

SUMMARY

The effect of ligation of the internal carotid artery in the neck in 17 cases of saccular aneurysms of the circle of Willis and in five cases of carotid-cavernous

sinus aneurysms is presented. Therapeutic benefit is evaluated in terms of improvement in local or neighborhood symptoms caused directly by the aneurysms. Eleven out of 14 patients with saccular aneurysms who showed such symptoms and all the patients with carotid-cavernous sinus aneurysms had sustained improvement in these symptoms. No deductions were possible regarding effect on life expectancy or recurrence rate. The procedure was ultimately tolerated well by at least 15 out of the 17 patients with saccular aneurysms and by all the patients with carotid-cavernous sinus aneurysms. The location of most of the saccular aneurysms in this group is assumed on anatomical evidence to be infraclinoidal.

CONCLUSION

Ligation of the internal carotid artery in the neck is usually a gratifying procedure when performed for unruptured infraclinoidal aneurysms of the circle of Willis in patients less than 50 years of age and for carotid-cavernous sinus aneurysms.

755 Fisher Building (Dr. Gass).

CLINICAL NOTES

PREPUBERTAL MALIGNANT MELANOMA

REPORT OF A CASE

Robert J. Coffey, M.D., Washington, D. C.
and
William T. Berkeley, M.D., New York

Malignant melanoma, originating from the common mole or nevus and characterized by a rapidly fatal course, is a relatively common neoplasm. According to Pack and his colleagues,[1] no person's body is without one or two nevi, and in some instances their number may exceed 100.

Age is most important in consideration of the presence or absence of malignancy in these lesions. Nevi showing apparent malignant change before the onset of puberty are called prepubertal or juvenile melanomas. These lesions present a microscopic picture consistent with malignancy but are not associated with demonstrable metastasis or blood vessel invasion. It is not uncommon to encounter a histopathology report of a growing nevus in a child indicating that the tissue is microscopically malignant, but probably clinically benign. Experience has taught that a melanoma occurring prior to puberty rarely, if ever, pursues a malignant course.[2] For this reason the diagnosis of malignant melanoma in prepuberty is at the present time seldom warranted.

Demonstrable metastases from prepubertal melanomas are rare. A search of the literature reveals only three reported cases in which metastasis to regional lymph nodes was identified. Webster, Stevenson, and Stout [3] encountered such a case in an 8-yr.-old girl. The primary lesion on the left shoulder was widely excised. Subsequent metastatic involvement of a cervical lymph node and the skin of the pectoral region occurred. After considerable delay because of refusal of further surgery a cervical and axillary dissection was carried out. Twelve years later the patient was living and well without evidence of further recurrence. In a 9-yr.-old female, her case reported by Spitz,[4] a primary melanotic lesion of the knee produced metastases to the nodes of both inguinal regions. Six months after excision of the melanoma, plus bilateral inguinal node dissection, the child was apparently well. MacDonald [5] reported a similar case of a 6-yr.-old male who had a "mole" removed from the knee. The pathologist reported cytological changes typical of malignant melanoma. Two weeks later, histopathologic study of enlarged ipsilateral inguinal and femoral nodes, removed by block dissection, showed metastatic involvement. Three years later the patient was apparently well, although nodules beneath the inguinal incisional scar were under observation.

The purpose of this paper is to present a case of true prepubertal melanoma with associated lymph node involvement and to discuss the significance of melanomas occurring before puberty.

REPORT OF CASE

N. C., a 7-yr.-old white female, was admitted to Georgetown University Hospital, Aug. 2, 1948, for treatment of a bluish lesion, measuring 1 cm. by 1 cm., overlying the sacrum in the mid-line. This pigmented area had been first observed by the child's parents one year previously; for the past three months there had been a noticeable increase in size. It was sharply demarcated, slightly elevated above the skin surface, and nontender, and the overlying skin appeared normal and intact. One discrete node in the left inguinal region was palpably enlarged.

On the following day, while the patient was under general anesthesia, this melanotic lesion with a generous margin of surrounding skin was excised, and at the same time the palpable left inguinal lymph node was removed. On transection of this node at the time of surgery, a subcapsular area of pigmentation was grossly discernible. The report of pathologic examination, rendered by Dr. C. F. Geschickter, was "malignant melanoma with lymph node metastasis." A review of the microscopic sections by several other pathologists confirmed this diagnosis.

On Sept. 4, 1948, with the patient under general anesthesia, a radical dissection of the femoral, inguinal, and iliac nodes, together with excision of a 3-in. (7.62 cm.) band of skin and subcutaneous tissue leading from the site of the primary lesion around to the groin, was performed on the left side. A similar procedure, but without removal of the iliac nodes, was carried out on the right side two weeks later. Meticulous examination of these excised nodes revealed no gross or microscopic evidence of metastasis. Lymphorrhea developed in the left inguinal incision, but disappeared one month postoperatively. Transient lymphedema of the left leg persisted for approximately three months. At the present time, 24 mo. postoperatively, the child is in apparent good health, with no evidence of recurrence (Figs. 1 and 2).

Professor of Surgery, Georgetown University School of Medicine (Dr. Coffey).
Former Resident in Surgery, Georgetown University School of Medicine (Dr. Berkeley).
From the Department of Surgery, Georgetown University Medical Center, Washington, D. C.

1. Pack, G. T.; Perzik, S. L., and Scharnagel, I. M.: California Med. **66**: 283, 1947.
2. (*a*) Ackerman, L. V.: Am. J. Clin. Path. **18**: 602, 1948. (*b*) Scharnagel, I. M.: J. Am. M. Women's A. **1**: 76, 1946.
3. Webster, J. P.; Stevenson, T. W., and Stout, A. P.: S. Clin. North America **24**: 319, 1944.
4. Spitz, S.: Am. J. Path. **24**: 591, 1948.
5. MacDonald, E. J., in The Biology of Melanomas, New York, the New York Academy of Sciences, 1948, p. 71.

ETIOLOGY

The neuroepithelial origin of the nevus has been well documented by histopathologic studies. Investigations of Soldan and, later, Masson have quite convincingly indicated the tactile organs of Meissner and Ranvier as the points of origin.[6] Pigmentation of nevi does not ordinarily occur until some time after birth, but it is generally believed that the cells are present prenatally.[7] Nevi may become pigmented throughout early life, but the greatest incidence occurs at or soon after puberty.

With the advent of puberty the incidence of malignant melanomas rises sharply, a fact that seems more than coincidental. According to Pack,[8] the hormonal activity associated with puberty is an important etiological factor in the production of malignant melanoma. It is noteworthy that no case of fatal malignant melanoma in prepuberty was found reported in the literature.

In order to be classified accurately as a prepubertal melanoma, the lesion must have occurred at an age sufficiently prior to the onset of puberty to eliminate the possibility of an early, clinically unmanifested gonadal influence. In like manner, melanomas appearing at or shortly after birth may have been influenced by maternal hormones; they are therefore eliminated from the true prepubertal class. Precocious development resulting from abnormal endocrine influences also precludes such a diagnosis.

Fig. 1.—Site of primary lesion marked by scars of bilateral en bloc dissection.

Of 13 cases of prepubertal melanoma reported by Spitz,[4] only one proved fatal. In the case of this 11-yr.-old female, it is questionable whether hormonal influence was not present in spite of the fact that the menarche had not been reached. MacDonald [5] reported the death of a 13-yr.-old girl from malignant melanoma of the vulva, but made no attempt to classify this case as prepubertal.

Weber and his associates [9] reported a case in which transplacental metastasis of a malignant melanoma to the fetus was demonstrated. Both the mother and baby died soon after delivery. The occurrence of true con-

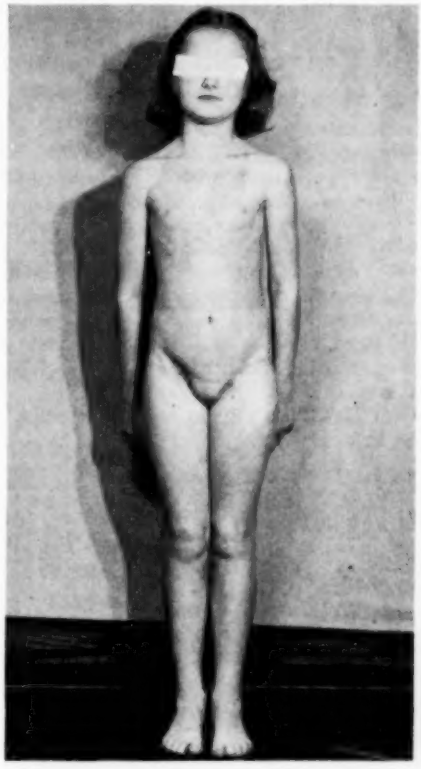


Fig. 2.—Scars of bilateral inguinal gland dissection.

genital malignant melanoma (that is, in which the mother is not the source of tumor) is extremely rare. Wells [10] considers a case reported by Coe [11] as the only well-documented and true example of such a case. These rare instances of malignant melanoma present at birth can be explained on the basis of maternal hormonal effect on the fetus.

Pregnancy appears to exert a stimulating influence on malignant melanoma, as shown by the rapidly fatal course of such cases. However, this same influence of pregnancy on other malignant tumors is well known. Further evidence of hormonal influence on the metabolic activity of nevi and melanin production is the increased degree of pigmentation of all melanin-bearing tissues during pregnancy. Pigmented nevi become darker in color, only to return to their original lighter color following pregnancy. This reaction is frequently seen in patients receiving large doses of estrogens.

With the onset of puberty there is an increase in the deposition of melanin about the genitals and the areolas of the breasts and in the number of nevi on the body. With the awakening of sex function during the mating

6. Foot, N. C.: Am. J. Path. **8**: 309, 1932.
7. MacKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer: A Practical Monograph, Philadelphia, Lea and Febiger, 1937, p. 56.
8. Pack, G. T.: Surg., Gynec. & Obst. **86**: 375, 1948.
9. Weber, F. P.; Schwarz, E., and Hellenschmied, R.: Brit. M. J. **1**: 537, 1930.
10. Wells, H. G.: Arch. Path. **30**: 535 (Aug.) 1940.
11. Coe, H. E.: Northwest Med. **24**: 181, 1925.

season of fish, frogs, and other animal life, there is an increase in melanophore activity. The work of Huggins on the effect of castration on malignant growth stimulated Herbst [12] and Howes [13] to employ castration in the treatment of advanced malignant melanomas. Both concluded that the rapid progress of the disease was not apparently affected.

PATHOLOGY

The detailed microscopic description of the tissue from the case reported above is as follows:

The primary tumor is dermal in location and is infiltrating the underlying fat. It is heavily pigmented with melanin. The tumor cells are apparently arising from nerve sheaths and in many places have an elongated spindle-cell shape (Fig. 3). These differentiate into cells with larger nuclei and more abundant cytoplasm with intracellular pigmentation. There are some tumor giant cells (Fig. 4). The histologic picture is that of malignant melanoma, in view of the morphology and infiltration of the fat. The histology resembles the so-called "melanosarcoma" which is related to nerve sheath. It is unusual at this age to encounter malignant melanomas, and even more unusual to see the sarcomatous variety. Those with carcinomatous appearance under the age of 14 have in my experience proved to be clinically benign.

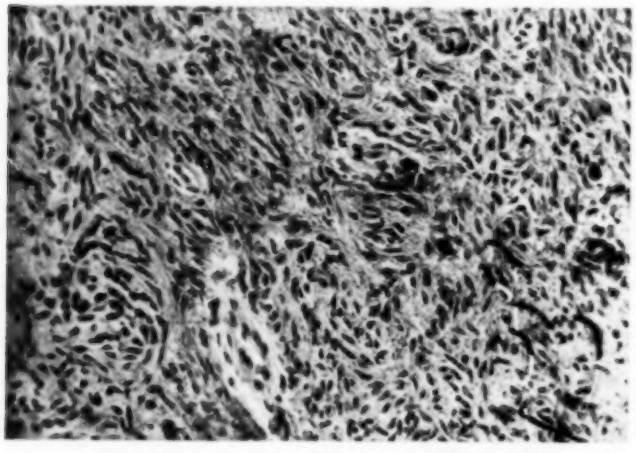


Fig. 3.—Spindle cell appearance of primary melanoma (× 80).

The lymph node shows four areas of pigment deposition under the capsule. The capsule is also involved. This pigment is melanin rather than hemosiderin. It is distributed among fibroblasts and macrophages. In one place, however, cells resembling those seen in the primary tumor are present along with the pigment (Fig. 5). In my opinion the pigment and tumor cells have been carried to the lymph node.

There are certain interesting differences between this case and the usual prepubertal melanoma. In this case there was no alteration in the normal overlying skin. Usually the epidermis overlying a prepubertal melanoma shows hyperkeratosis and occasional areas of parakeratosis. Acanthosis is also characteristic. In this case there were no junctional or epidermal-dermal features like those usually seen in the prepubertal lesion. These characteristic changes are a lack of uniform palisading of the basal layer, abrupt transition from epidermis to tumor, and large collections of giant cells and pigment. In this case there was no close association between the tumor and the overlying epidermis or its adnexal elements. In prepubertal melanoma the more anaplastic elements are usually junctional in location, with a tendency toward uniformity in the deep portions of the lesion, whereas in this case the anaplastic elements were deeply located, with greater uniformity in the more superficial areas. It is the opinion of Geschickter [14] that the sarcomalike cellular structure found in this melanoma is more characteristic of the adult variety and is rarely found in the prepubertal group.

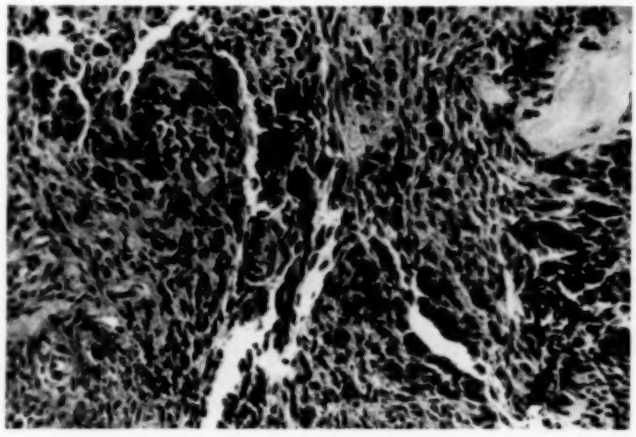


Fig. 4.—Numerous melanin-containing giant cells in primary melanoma (× 80).

Spitz,[4] in seeking microscopic differences between prepubertal and adult melanomas, found giant cells to be the most distinctive feature in eight of 13 cases of the former. Giant cells are not conspicuous in the adult variety. She concluded that large numbers of giant cells are suggestive of a prepubertal lesion, and that their occurrence in the adult variety is a favorable prognostic sign.

COMMENT

The objection may be raised that in the case reported the pigment was carried to the regional lymph node by giant cells. Harding and Passey,[15] using melanoma-bearing rats, proved that phagocytized pigment does appear in lymph nodes without the concurrent presence of malignant cells. Distant spread of melanin in adult melanomas without malignant cells in the same area does occur. According to Ackerman [2a] the same is true

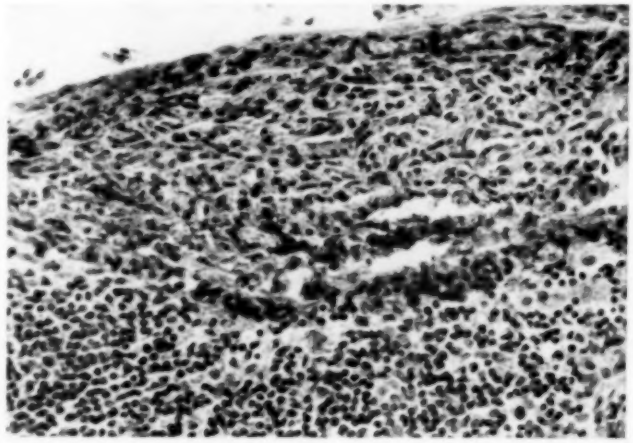


Fig. 5.—Inguinal lymph node showing a subcapsular area of melanin-containing tumor cells (× 80).

12. Herbst, W. F.: J. A. M. A. **122**: 597 (June 26) 1943.
13. Howes, W. E.: Radiology **43**: 272, 1944.
14. Geschickter, C. F.: Personal communication to the authors.
15. Harding, H. E., and Passey, R. D.: J. Path. & Bact. **33**: 417, 1930.

of nevi. This, then, would serve as a reasonable explanation for the appearance of pigment in a lymph node in association with a prepubertal melanoma that in itself is considered benign. It does not, however, explain the appearance in a regional lymph node of cells that are similar to those of the primary melanotic lesion.

The dopa staining reaction was not performed in this case on the involved lymph node to distinguish between melanoblasts (malignant cells) and melanophores (phagocytes). Likewise such studies were not carried out in the cases of Webster and his colleagues,[3] Spitz,[4] and MacDonald.[5] Without the demonstration of melanoblasts by a positive dopa reaction, the final diagnosis of malignant melanoma may not seem warranted in the minds of some.

It is interesting to speculate that the cells of the primary lesion and the involved lymph node in this and similar cases may be of low-grade malignancy, destined to remain relatively static until stimulated by some hormonal influence with the onset of puberty. We are inclined to accept this and the three similar cases as true examples of prepubertal malignant melanoma. A favorable prognosis is likely in this case, in view of the course of the other, similar, cases and because of the general nature of prepubertal lesions.

TREATMENT

The treatment of melanomas, based on sound surgical principles, has been outlined by Pack and associates.[16] Nevi occurring before puberty and prepubertal melanomas should be removed for prophylactic reasons. Those occurring on the feet, legs, hands, scalp, about the genitals, and in the future bearded areas of males are subjected to the greatest amount of trauma and irritation and are the commonest sites of malignant melanomas. Removal by surgical excision is desirable. A wide excision with a liberal margin of healthy skin is essential. Incisional biopsies are to be condemned.

Prepubertal melanomas with lymph node involvement should be surgically handled in the same manner as adult lesions. Wide excision of the primary lesion, plus radical regional lymph node dissection, together with en bloc removal of an adequate strip of intervening skin, subcutaneous tissue, and fascia, is the treatment of choice when possible. However, in cases of prepubertal malignant melanoma of distal parts of the extremities, where dissection by continuity is not practicable, amputation is not warranted in view of the absence of fatalities from prepubertal lesions. In such instances wide local excision of the primary lesion with a radical inguinal or axillary node dissection is recommended. A two-week to three-week interval between removal of the primary lesion and gland dissection is advised by some on the grounds that complete emptying of the intervening lymphatics should take place before the filtering regional nodes are excised.

SUMMARY

A case of prepubertal malignant melanoma with lymph node metastasis was added to three previously reported similar cases. A review of the literature with a discussion of the etiology, pathology, and treatment of these lesions was presented.

3900 Reservoir Road N. W.

16. Pack, G. T.; Scharnagel, I., and Morfit, M.: Surgery **17**: 849, 1945.

LEFT-UPPER-QUADRANT GALLBLADDER

Alan R. Bleich, M.D.
Donald O. Hamblin, M.D.
and
Dorothy Martin, R.N., New York

Although several anomalies of the gallbladder are well known, a localization in the left upper quadrant of the abdomen, in the absence of situs inversus, is a rarely described situation of sufficient roentgenologic, medical, and surgical interest to merit a review of 11 reported cases and the account of a 12th. The case to be presented is the fourth found preoperatively by radiographic methods.

REPORT OF A CASE

A male office worker, 28, was examined because of flatulence and chronic upper-abdominal distress. The patient's complaint was first recorded three years prior to the present examination. At that time there was a history of moderate weight loss and pain in the upper abdomen. A roentgen examination of the gallbladder was made. The patient was then informed by a physician that the gallbladder failed to appear on the radiograms and that it was nonfunctioning. Since that time the patient has repeatedly experienced flatulence and a bloated sensation in the abdomen in the morning. The appetite had been poor, but the bowel habits were regular. There were no headaches. He reported colicky pains in the abdomen after eating fried foods; the pain diminished markedly after omission of these foods. Ingestion of milk or cream caused discomfort, but butter did not. A weight loss of 18 lb. (8.2 kg.) took place over a four-year period. In 1941 a severe attack of abdominal colic was attributed to the consumption of 3 qt. (3,000 cc.) of milk a day for three months. An appendectomy had been performed in 1940 after three bouts of abdominal colic.

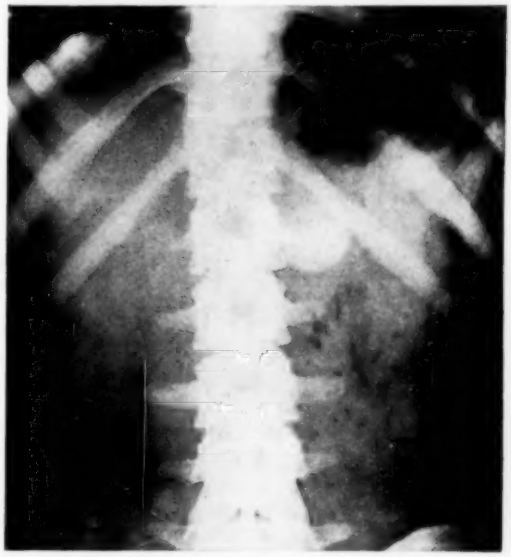


Fig. 1.—Posteroanterior radiograph of the abdomen. The gallbladder is on the left side at the level of the left transverse process of the first lumbar vertebra. The gas bubble in the stomach is on the same side of the abdomen as the gallbladder.

A roentgen examination of the gallbladder was made on March 31, 1950. Fifteen hours following oral ingestion of the dye, the gallbladder was visible in the left upper quadrant at the level of the first lumbar vertebra, overlapping the left transverse process of this vertebra. This is an unusual position for the gallbladder and presumably accounts for the previous diagnosis of "nonfunctioning" gallbladder. There was no evidence of situs inversus. The size and shape were normal, and there was no filling defect. Concentration of the dye was satisfactory. After

ingestion of a fatty meal, the gallbladder contracted. A gastrointestinal series was done. Fluoroscopic and radiographic examination of the upper gastrointestinal tract showed normal position and structure of the esophagus, stomach, and duodenum. No evidence of intrinsic filling defect or ulceration could be seen. Peristalsis was within normal limits. In five hours the stomach was empty and barium had reached the descending colon. The transverse colon occupied a low position. The roentgenographic examination disclosed no abnormalities, and a fluoroscopic examination of the chest failed to reveal evidence of a pulmonary or cardiac anomaly. The patient was treated by diet and the use of dehydrocholic acid (decholin®). No immediate surgery was considered necessary.

Gallbladder anomalies have been enumerated by Schachner,[1] Lichtman,[2] and others. Lockwood's [3] listing of congenital abnormalities of the gallbladder and ducts is the most inclusive to date:

1. Anomalies of the form of the gallbladder are the phrygian cap, liberty cap, or folded fundus gallbladder, the fishhook type, and the type which is partitioned by a lobe or diverticulum.
2. Anomalies of number are the absent, rudimentary, and double gallbladder.

Fig. 2.—Posteroanterior view of the abdomen after ingestion of a fatty meal. The gallbladder is contracted to one-third of its original size.

3. Anomalies of the position of the gallbladder are the intrahepatic, the floating or ptotic, and the left-sided gallbladder, which is either on the under surface of the left lobe of the liver or situs inversus.
4. Anomalies of the cystic duct are absence, stricture, reduplication, and abnormal termination into the stomach.
5. Anomalies of the hepatic and common ducts are absence, stricture, reduplication, and abnormal termination into the stomach.
6. Anomalies of the hepatic and cystic arteries are double cystic artery and abnormal relation of the hepatic artery to the cystic duct.

Simkins [4] states that the gallbladder, cystic duct, and common bile duct arise with the ventral pancreas from the endodermic bud of the liver. The middle enlargement of the hepatic rudiment, destined to form the gallbladder, is solid in embryos of 4.9 mm.; soon afterward the gallbladder cells form a lumen. The cystic duct remains solid but becomes interspaced with minute separations throughout its short course. In embryos of 16 mm. the cystic duct and the common bile duct are open throughout. As the liver moves to the right, the gallbladder expands and follows, pulling the left umbilical vein to the median line.

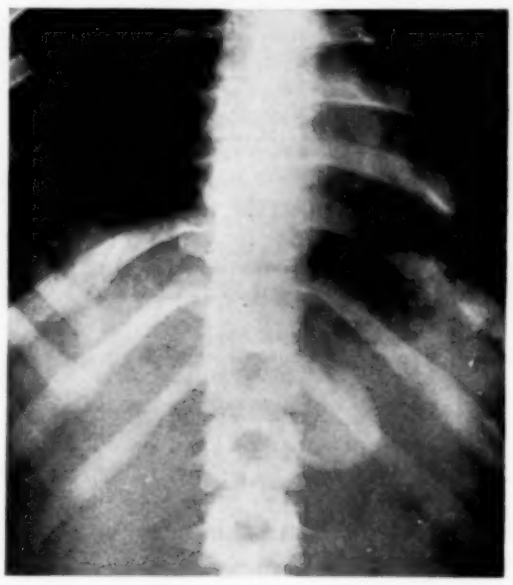


Fig. 3.—The gallbladder shadow after a double dose of iodoalphionic acid ("priodax") is larger and more distinct than that seen after a single dose. This view is centered high enough to demonstrate the heart shadow on the same side as the gallbladder.

Fig. 4.—Right anterior oblique radiograph of the abdomen after the administration of a fatty meal. The left-sided gallbladder has now contracted. It is seen well on the side opposite the main shadow of the liver.

The embryology of a left-sided gallbladder in association with situs inversus is not of special interest. The left-sided gallbladder as a solitary phenomenon, however, presents a problem with respect to developmental history. Gross [5] suggests that a gallbladder can develop

1. Schachner, A.: Anomalies of the Gallbladder and Bile Passages, with Report of a Double Gallbladder and a Floating Gallbladder, Ann. Surg. **64**: 419-433, 1916.
2. Lichtman, S. S.: Diseases of Liver, Gallbladder and Bile Ducts, Philadelphia, Lea & Febiger, 1942, p. 786.
3. Lockwood, B. C.: Congenital Anomalies of Gallbladder, J. A. M. A. **136**: 678-679 (March 6) 1948.
4. Simkins, C. S.: Textbook of Human Embryology, Philadelphia, F. A. Davis Company, 1931, p. 356.
5. Gross, R. E.: Congenital Anomalies of Gallbladder: Review of 148 Cases, with Report of Double Gallbladder, Arch. Surg. **32**: 131-162 (Jan.) 1936.

under the left lobe of the liver in one of two ways. If the ectopic gallbladder has a normally located exit by way of the cystic duct, it most probably arose as a normal embryologic bud from the hepatic diverticuli. Gross purposes that instead of assuming a normal position under the right lobe of the liver, such a gallbladder migrated to a position under the left lobe and therefore retained a normally implanted and attached cystic duct. With the development of the peritoneum, the gallbladder then remained fixed to the left of the falciform ligament. Such an origin seems probable in the cases described by Walton [6] and Harris.[7] In each of these the cystic duct arose from the junction of the hepatic and common duct, was directed forward and to the right toward the normal fossa of the gallbladder, and then took a sharp hairpin turn toward the left, where it was passed on the left by the falciform ligament. A gallbladder on the left side may also be explained as a second gallbladder directly from the hepatic duct. This process, accompanied by a lack of development of the normal structure on the right side, appears to have occurred in the first example recorded by Kehr.[8] A detailed account of the embryology of the liver and gallbladder is given by Huntington.[9]

When the gallbladder lies under the left lobe of the liver, it is located on the left of the ligamentum teres and the peritoneal reflection of this ligament, which forms the falciform ligament of the liver. These ligaments effectively screen a left-sided gallbladder from the view of a surgeon, who may be unaware of this anomaly and may fail to explore the left lobe of the liver in the event that a gallbladder is not found in the right upper quadrant. Since this problem may also influence the choice of an appropriate incision, a preoperative roentgen diagnosis may be most helpful. A case is described by Walton [6] in which the left-sided gallbladder was wholly obscured by the falciform ligament. The gallbladder if approached from the right at operation, would have been entirely hidden.

It would be desirable if specific signs or symptoms could be recognized which would distinguish left-sided gallbladder disease. In this connection, it may be noted that Hartung's [10] patient complained of a slightly painful sense of pressure over the entire epigastric area. Biancheri's [11] patient had tenderness to palpation at a point midway between the xiphoid and the umbilicus and no tenderness in the right upper quadrant; however, the diagnosis was complicated by the presence of a gastric ulcer. The patient described in this report had no localizing symptoms and no radiographic evidence of gallbladder disease. The problem of whether a pathological left-sided gallbladder will actually produce left-sided discomfort remains unsolved, although such left-sided discomfort appears probable. The differentiation of duodenal or gastric disease from disorders of a left-sided gallbladder is a diagnostic problem that might be decided by roentgen examination.

The radiographic aspects of a left-sided gallbladder are well illustrated in the preceding case report. Roentgenograms had previously been taken for detection of possible gallbladder disease. The roentgenograms taken were all of the 10 by 12 in. size, and the area covered was the right upper quadrant. By this conventional technique a left-sided gallbladder had been completely excluded from the field of view, and the examination was reported as failing to demonstrate concentration of dye by the gallbladder. Three years later a 14 by 17 in. roentgenogram disclosed the actual whereabouts and presence of a normally functioning gallbladder.

Gross,[5] in his comprehensive survey of congenital anomalies of the gallbladder, notes that in all cases the gallbladder lay to the left of the round and falciform ligaments. Where the falciform ligament was very broad, the gallbladder was hidden from view through a conventional incision in the right upper quadrant. Whipple [12] advises that the surgeon be alert for such anomalies and variations. Absence of the gallbladder from the right upper quadrant of the abdomen, as demonstrated by surgery, has been interpreted as atrophy or extreme fibrosis of the gallbladder following inflammatory disease, congenital absence of the viscus, or a completely intrahepatic gallbladder. To this differential diagnosis we must also add the possibility that the gallbladder is located on the left side of the abdomen. A preoperative diagnosis may avoid difficulty at the operating table in the case of a left-sided gallbladder requiring differentiation from atrophy or extreme fibrosis of the gallbladder following inflammatory disease, or from congenital absence of the viscus, or from a completely intrahepatic gallbladder.

SUMMARY

A normally functioning left-sided gallbladder, not associated with situs inversus or other known anomalies, was found by roentgen methods in a man, 28, with recurrent, mild upper-abdominal pain. The ectopic gallbladder shadow was demonstrated on a 14 by 17 in. radiogram after it had failed to appear on conventional smaller size roentgenograms of the right upper abdominal quadrant. Reference is made to 11 previous reports of diagnostic and surgical problems encountered in patients whose gallbladders were on the left side.

1056 Fifth Ave. (Dr. Bleich).

6. Walton, A. J.: Congenital Malposition of Gallbladder, Lancet **1**: 925, 1912.

7. Harris, H. A.: Intrapelvic Ectopic Testis Combined with Ectopia Vesicæ, Congenital Umbilical Hernia and Abnormal Gallbladder: A Rare Case, Arch. Surg. **13**: 644-654 (Nov.) 1926.

8. Kehr, H.: Seltene Anomalie der Gallengage, Muench. Med. Wchnschr. **49**: 229, 1902.

9. Huntington, G. S.: Anatomy of Human Peritoneum and Abdominal Cavity Considered from Standpoint of Development and Comparative Anatomy, Philadelphia, Lea Brothers & Company, 1903.

10. Hartung, A.: Linksgelagerte Gallenblase im Röntgenbild, Röntgenpraxis **4**: 392-394, 1932.

11. Biancheri, T.: Colecisti a sinistra, Arch. ital. chir. **69**: 415-420, 1947.

12. Whipple, O.: Surgery of Biliary Tract, in Nelson New Loose-leaf Surgery, New York, Thos. Nelson & Sons, 1932, Vol. 5, p. 458.

Scurvy.—The Hispanic-American contribution to the history of scurvy is of the utmost importance. Since 1579 Farfan recommended the juice of citrus fruits for the treatment of ulcers of the gums undoubtedly of scorbutic origin, recommendations which he again proposed in his Mexican books in 1592 and 1610. In 1623 in Lisbon, Abreu talks about scurvy, and also Esteyneffer gives an exact account of scurvy and its treatment in Mexico in 1712, half a century before Lind. On the other hand, the treatises of Lardizabal, which were printed in Spain in 1764 for the Society of Caracas in Venezuela, and that of Corbella, ancient lieutenant physician of Tucuman, La Plata River, and also of Paraguay, printed in Madrid 1794, give important information. The latter one points out that scurvy is a disease due to the use of an improper diet in which some essential factors are lacking.—Francisco Guerra, Hispanic-American Contribution to the History of Scurvy, *Centaurus*, No. 1, 1950.

ENDOMETRIOSIS OF CERVIX UTERI WITH FORMATION OF LARGE ENDOMETRIAL CYST

REPORT OF A CASE

Vernon H. Plager, M.D.
Harry M. Nelson, M.D.
and
Donald C. Beaver, M.D., Detroit

Much has been written, during the past three or four decades, on the subject of endometriosis. The theories of pathogenesis and clinical considerations of the disease have been repeatedly studied and reviewed so that there is little to add to existing literature except unusual or variant features.

The case to be presented is that of an unusually large, hemorrhagic, endometrial cyst which developed in the posterior wall of the cervix uteri, extending posteriorly to form a mass filling the rectovaginal pouch. The unusual site and large size of the cyst make the case almost unprecedented in the literature on endometriosis.

REPORT OF CASE

The patient was a 50-year-old married woman admitted to Woman's Hospital on the gynecological service of Dr. H. M. Nelson, Aug. 18, 1948. Her chief complaint on admission was acute right lower quadrant and low back pain of two days' duration. On Aug. 16, the dull, persistent low back pain was first noticed. The following day the pain shifted to the right lower quadrant. The abdominal pain was constant, sharp and severe in character, and not associated with nausea or vomiting. The morning of Aug. 18, the pain was still present and increasing in severity. Her bowels moved normally and there were no urinary complaints. On the afternoon of Aug. 18, the patient was seen by her physician. Medication prescribed at this time failed to relieve her pain. She was again seen that same evening and hospitalized with a tentative diagnosis of pelvic abscess.

Details of her past history, save those relating to menstruation, were noncontributory. There was no history of previous surgical procedures.

The menarche occurred when the patient was 15. Her periods had always been regular, occurring every 28 days until 1943. The menstrual flow had always been heavy, lasting for 7 days. The patient stated that the flow was usually so profuse that she had to make and use pads that were larger and thicker than the commercial types. She denied any history of dysmenorrhea, except for occasional cramps and backache. In April, 1943, she consulted her family physician because of profuse menstrual flow every two to three weeks during the previous three months. Pelvic examination in 1943, as recorded by her physician, revealed an enlarged, boggy, retroverted uterus, and an enlarged right ovary. There was no record of any retrocervical mass. The patient was treated with estrogens and her menstrual cycle was corrected. Ferrous sulfate therapy was also carried out for a secondary anemia (hemoglobin 61%). On the present admission she stated that she had been menstruating irregularly for the past year, with a decrease in the amount and duration of flow. Her last menstrual period was four months prior to the present illness. She gave no history of pregnancies.

The family history was noncontributory.

Physical examination on admission revealed a well-developed, well-nourished white woman, who appeared to be in acute distress. The temperature was 99.8 F.; the blood pressure was 128/84; the pulse rate was 100. The physical examination was essentially negative except for the abdominal and pelvic examinations.

The abdomen was soft and nontender. The solid viscera were not palpable. In the right lower quadrant there was a palpable mass, which was irregular, firm, movable, and the size of a small orange.

Pelvic examination demonstrated the cervix to be pointing anteriorly and pushed up behind the symphysis. There was a large, firm, rounded, semifluctuant, grapefruit-sized tumor filling the cul-de-sac. Also, there was a movable tumor in the right lower quadrant, thought to be a subserous uterine myoma.

Laboratory studies revealed the following: normal urine; hemoglobin 11.5 gm. per 100 cc. of blood; red blood cells 4,160,000 per cubic millimeter of blood, and white blood cells 24,500 per cubic millimeter of blood. The differential white blood count revealed 85% neutrophils (64% filamented and 21% nonfilamented), 13% lymphocytes, and 2% monocytes. The blood serology was negative. A photoroentgenogram of the chest disclosed a healed primary tuberculous lesion.

The preoperative diagnosis was (1) leiomyomas of the uterus, (2) possible ovarian cyst with torsion of the pedicle, and (3) possible pelvic abscess.

The morning following admission to the hospital, the patient was taken to the operating room. With the patient under spinal anesthesia, pelvic examination was repeated. The findings were essentially the same as those of the admission examination. The mass in the cul-de-sac seemed to be free and moved with the mass in the right lower quadrant. While the pelvic examination was being done there was a sudden gush of chocolate-colored blood from the vagina. The decision to do a laparotomy was made, and no further procedures were carried out from below.

The abdomen was opened through a suprapubic paramedian incision. Exploration of the upper abdomen was essentially negative.

In the pelvis, the ovaries were found to be small and sclerotic. The uterus was pushed anteriorly and to the right by the mass in the cul-de-sac. The uterus was enlarged and irregular. The mass which had been palpated preoperatively in the right lower quadrant was the fundus uteri. Behind the uterus in the cul-de-sac was a large, smooth-walled, cystic, grapefruit-sized mass. There were some adhesions in the cul-de-sac, which were easily freed. Total hysterectomy, including the cystic mass, and a bilateral salpingo-oophorectomy were performed. When the uterus was removed there was a large amount of chocolate-colored blood in the vagina. An appendectomy was done and the abdomen was then closed in layers.

The postoperative diagnosis was (1) multiple leiomyomas of the uterus, (2) large endometrial cyst of the uterus or degenerated leiomyoma.

The postoperative course of the patient was uneventful. She was discharged from the hospital in good condition on the 14th postoperative day.

PATHOLOGICAL REPORT

The entire specimen, consisting of the uterus, cervix, both tubes, both ovaries, and the large cervical mass, weighed 199 gm. (Figs. 1 and 2). The uterus and cervix measured 10 by 5.5 by 4 cm. A rounded, smooth, grayish-white mass, in the partially collapsed state, measuring 8 by 7.5 by 5 cm., extended from the posterior wall of the cervix in a bulbous manner. On sectioning, the wall of the mass appeared to be continuous with the posterior wall of the lower uterine segment and the cervix. The mass was centrally occupied by a unilocular space with a small rounded opening (Fig. 1) from the central cavity into the cervical canal at or near the level of the internal cervical os. It was through this opening that the chocolate-colored material was partially evacuated from the cyst at the time of vaginal examination. The cyst still contained a considerable quantity of thick, pasty, chocolate-colored material. There was a considerable amount

From the Departments of Gynecology and Pathology, Woman's Hospital.

This article has been abbreviated for publication in THE JOURNAL by omission of figures 1, 2, 4, 5, 6, and 7. These will appear in the Author's reprints.

of brownish-black pigment intimately adherent to the relatively smooth lining of the cyst wall (Fig. 3). The wall of the cyst was uniformly thick throughout, measuring from 5 to 8 mm., in thickness, and had the usual consistency of the cervical muscular coat.

The myometrium measured 2 cm. in greatest thickness. Within the myometrium there were multiple, small, nonencapsulated, soft, grayish-pink areas which had the gross appearance of adenomyosis uteri. Also, there were multiple, small, well-encapsulated, pinkish-white, firm tumor nodules in intramural and subserous positions (Fig. 2). These had the gross appearance of leiomyomas and all measured 1.5 to 2 cm. in diameter. The ovaries were small and sclerotic, and revealed multiple, small, thin-walled, brownish-black simple cysts. These small cysts all measured less than 1 cm. in diameter. The contents of these ovarian cysts were soft, pasty, chocolate-colored material.

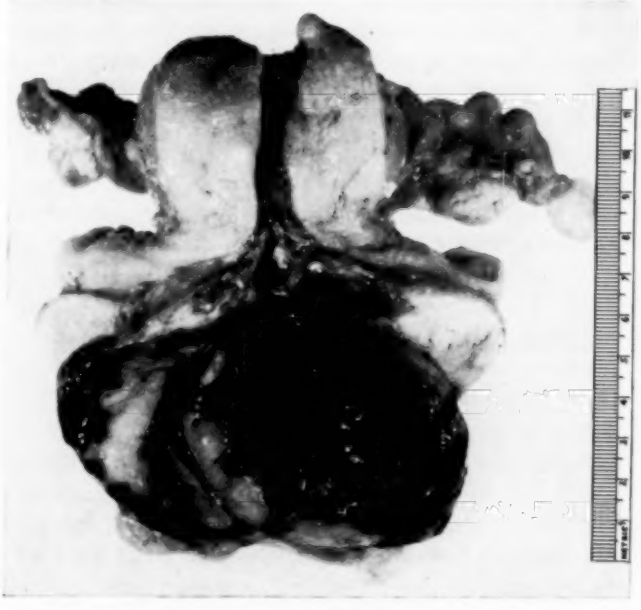


Fig. 3.—Anterior view of the specimen, which was opened by incision through the posterior lip of the cervix and the cyst wall. Old blood intimately adherent to the lining of the cyst can be seen.

Microscopic sections showed the cervical cyst to be lined with low, columnar epithelial cells with well-defined, dark-staining basilar nuclei typical of endometrium. Underlying this and forming its support, there was typical cytogenic endometrial stroma (Fig. 4). In the stromal layer there were scattered neutrophils and small vessels. Deeper in the cyst wall there were larger vessels and fibrous connective tissue irregularly arranged. Smooth muscle bundles were seen mixed with the fibrous connective tissue of the cyst wall, giving the typical appearance of the musculofibrous architecture in the wall of the lower uterine segment and cervix. There was also evidence of hemorrhagic extravasation into the cytogenic stroma and deeper layers of the cyst wall, as demonstrated by the blood pigments phagocytized in histiocytes (Fig. 5).

Microscopic studies of the uterine wall disclosed endometrial glands deep in the myometrium (Fig. 6). The ovaries revealed multiple small endometrial cysts (Fig. 7), lined with typical low columnar or cuboid endometrial-type epithelium surrounded or supported by cytogenic endometrial stroma.

The complete pathological diagnosis was as follows: (1) endometriosis of the cervix, with a large chocolate-type endometrial cyst of the posterior wall, communicating through a sinus with the cervical canal; (2) chronic cervicitis, with erosion and squamous epithelial metaplasia; (3) proliferative phase endometrium; (4) adenomyosis of the uterus; (5) multiple intramural and subserous leiomyomas of the uterus; (6) sclerosis of the ovaries, with endometriosis and chocolate-cyst formation.

DISCUSSION

The incidence of endometriosis appears to vary greatly. It has been reported as low as 1.62% by Fallas and Rosenblum [1] in review of their gynecologic operations. Lewinski [2] reported an incidence of endometriosis interna of 53.5%. Meigs [3] found endometriosis in 28% of gynecologic operations among private patients, and 5.8% in 400 consecutive gynecologic operations at Massachusetts General Hospital. The variation in incidence is equally as great as reported by Sampson,[4] Dreyfuss,[5] Holmes,[6] Haydon,[7] and Brines and Blain.[8]

Although there are many reports in the literature on the incidence and theories of the etiology of endometriosis, there is little written concerning the size of endometrial cysts. Novak [9] states that these cysts rarely reach a "large size, being sometimes very tiny and rarely larger than a hen's egg." He also states that the largest endometrial cysts that he has seen are about the size of a large orange. Haydon [7] also comments that endometrial cysts are usually no larger than a hen's egg. Novak explains that large endometrial cysts arising in foci of external endometriosis are rare because such lesions have a tendency to perforate early.

Gold and Kearns,[10] in their study of cystic adenomyosis of the uterus, comment that the pathogenesis of the cysts was on the basis of misplaced remnants of Müllerian duct epithelium, or as a result of lymphatic or hematogenic spread of endometrium into the myometrium. Thus, there would be no connection between the glands embedded in the myometrium and the glands of the endometrium. In 1908, Cullen [11] demonstrated in 55

1. Fallas, R., and Rosenblum, G.: Endometriosis: A Study of 260 Private Hospital Cases, Am. J. Obst. & Gynec. **39**: 964, 1940.

2. Lewinski, W., cited by Zaleski, W.: Adenomyosis experimentalis nach Interruptio graviditatis durch Curretage bei Kaninchen, Zentralbl. f. Gynäk. **60**: 1046, 1936, cited by Brines, O. A., and Blain, J. H.: Adenomyosis of the Uterus, Surg., Gynec. & Obst. **76**:197, 1943.

3. Meigs, J. V.: Endometriosis: Its Significance, Ann. Surg. **114**: 866, 1941.

4. Sampson, J. A.: Benign and Malignant Endometrial Implants in the Peritoneal Cavity, and Their Relation to Certain Ovarian Tumors, Surg., Gynec. & Obst. **38**: 287, 1924, cited by Meigs, J. V.[3]; Endometrial Carcinoma of the Ovary, Arising in Endometrial Tissue in That Organ, Arch. Surg. **10**: 1 (Jan.) 1925, cited by Meigs, J. V.[3]

5. Dreyfuss, M. L.: Pathological and Clinical Aspects of Adenomyosis and Endometriosis, Am. J. Obst. & Gynec. **39**: 95, 1940.

6. Holmes, W. R.: Endometriosis, Am. J. Obst. & Gynec. **43**: 255, 1942.

7. Haydon, G. B.: A Study of 569 Cases of Endometriosis, Am. J. Obst. & Gynec. **43**: 704, 1942.

8. Brines, O. A., and Blain, J. H.: Adenomyosis of the Uterus, Surg., Gynec. & Obst. **76**: 197, 1943.

9. Novak, E.: Gynecological and Obstetrical Pathology with Clinical and Endocrine Relations, ed. 2, Philadelphia, W. B. Saunders Company, 1947.

10. Gold, S., and Kearns, P. J.: Cystic Adenomyosis of the Uterus, Am. J. Obst. & Gynec. **52**: 840, 1946.

11. Cullen, T. S.: Adenomyoma of the Uterus, Philadelphia, W. B. Saunders Company, 1908, cited by Brines and Blain.[8]

of 56 cases of adenomyomatous uteri that the gland elements of the ectopic tissue were derived from, and usually were a direct continuation of, endometrial glands. Thus Cullen explained the rarity of endometrial cyst formation in the uterine wall.

In the case reported here, it is our belief that the large endometrial cyst arose from endometriosis in the posterior wall of the cervix above the fornix vaginae or from the lower uterine segment, rather than from foci of endometriosis in perimetrial positions, secondarily invading the cervix. This opinion is supported by the fact that the cyst wall is intimately continuous with the wall of the cervix and lower uterine segment, by the relative ease with which the cyst was bluntly dissected free from the surrounding structures other than the uterus and cervix, and by the microscopic structure of the cyst wall. If we are correct in assuming the site of origin of this endometrial cyst, it is of considerable interest. Focal endometriosis occurs in the wall of the cervix and in the lower uterine segment. However, we have been unable to find anything in the literature on the occurrence of large cysts arising from endometriosis located at this site, or in the other portions of the uterus. Almost invariably the site of origin of large endometrial cysts is the ovaries.

Endometrial cysts of the ovaries are usually thin-walled and friable and are frequently adherent. Consequently, any exacting study of the size attained by such cysts is difficult because so many are ruptured in the process of removal. However, it is our impression that, although these cysts are usually no larger than 5 to 6 cm. in diameter, not infrequently they are considerably larger. We have seen endometrial cysts of the ovary that are 10 to 11 cm. in diameter, the size of a grapefruit. The endometrial cyst reported here was felt to be the size of a large grapefruit prior to its partial evacuation at the time of examination at operation.

The pathogenesis of the cervical endometriosis and endometrial cyst reported is probably best explained by the theory of Gold and Kearns [10] in their study of cystic adenomyosis of the uterus, since it is apparent that there were no connecting glands between the embedded endometrial glands in the wall of the cervix and cervical gland lumens. Generally, such connections do exist, substantiating the theory of Cullen[11] and their existence explains the rarity of cyst formation in this type of endometriosis. It may also be contended that in our case connecting glands between the cervical endometriosis and the cervical gland lumens originally existed, but, because of the anatomic location, these were obliterated, allowing retention of products of menstruation in the area of endometriosis with eventual cyst formation.

SUMMARY

The case reported is that of an unusually large endometrial cyst of the cervix uteri, associated with cervical endometriosis. The cyst presented posteriorly and filled the rectovaginal space in such a manner that the diagnosis of pelvic abscess was first entertained. Although the cyst had undoubtedly been present for a considerable time, the onset of related symptoms was acute, consisting of severe lower abdominal and back pain.

432 E. Hancock Ave.

PRIMARY CARCINOMA OF THE APPENDIX

A REPORT OF TWO CASES

Robert J. Sillery, M.D., New Orleans

Primary carcinoma of the appendix was discussed by Ewing (1940)[1] and by Willis (1934 [2] and 1948 [3]), but the important original papers are those of Rolleston and Jones (1906),[4] who accepted 42 previously reported cases of primary carcinoma of the appendix, and Uihlein and McDonald (1943),[5] who described 5 cases from the Mayo Clinic. Phillips and Isaac (1930)[6] reported a single case in which the tumor involved the omentum and ileum as well as the appendix. Willis (1948)[3] investigated 13 cases of appendiceal tumors, but found 11 of these were argentaffin, or carcinoid tumors. The true adenocarcinoma of the appendix seems to be a rare tumor, and according to Willis (1948)[3] it shares the age incidence, structure, and behavior of its counterparts in the colon. Mucus secretion is often a conspicuous characteristic, and his observation that caecal carcinoma may invade the appendix, or may cause obstructive appendicitis, must be kept in mind in the pathological diagnosis of surgical specimens. Ewing (1940)[1] states that of 13,083 appendices included in the lists of Batzdorff and McCarthy (from the Bender laboratory) there were 60 cases of primary carcinoma of the appendix—an incidence of 0.45%. Lesnick and Miller (1949)[7] from the Mount Sinai Hospital in New York reported five cases and reviewed the records of 12 others previously reported in the literature. Bosman and Wierberdink (1949)[8] from the Netherlands described a single case.

This brief review of the literature demonstrates that primary carcinoma of the appendix is not rare, since the above yields a total of 116 cases from only seven sources. Only those references that clearly differentiated between primary adenocarcinoma and carcinoid were used in this review.

It is desirable to report further cases of malignant disease of the appendix for two reasons: (1) clinically, it usually produces no symptoms, and small carcinomas are usually found in appendixes excised with other preoperative diagnosis, and (2) it is an unusual tumor for which, because of its rarity, little prognostic information is available to the clinician.

From the Laboratory of Pathology and Pharmacology, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, Federal Security Agency.

1. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, Philadelphia, W. B. Saunders Company, 1940, p. 725.

2. Willis, R. A.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, Ltd., 1934.

3. Willis, R. A.: Pathology of Tumors, London, Butterworth & Co., Ltd., 1948, pp. 426-427.

4. Rolleston, H. D., and Jones, L.: Primary Malignant Disease of the Vermiform Appendix, Am. J. M. Sc. **131**: 951, 1906.

5. Uihlein, A., and McDonald, J. R.: Primary Carcinoma of the Appendix Resembling Carcinoma of the Colon, Surg. Gynec. & Obst. **76**: 711, 1943.

6. Phillips, E. W., and Isaac, D. H.: Primary Carcinoma of the Appendix, Brit. M. J. **1**: 1127, 1930.

7. Lesnick, G., and Miller, D.: Adenocarcinoma of the Appendix, Cancer **2**: 18, 1949.

8. Bosman, G., and Wieberdink, J.: Primair carcinoom van de appendix op jarige icefijd, Nederl. tijdschr. v. geneesk **93**: 3980, 1949.

REPORT OF CASES

CASE 1.—A white man aged 55, who had had no previous complaints referable to the gastrointestinal tract, returned home from work and did not eat dinner because of slight nausea. He retired early that evening but was awakened from his sleep during the night by rather severe right lower quadrant pain. On his admission to the hospital, localized pain, tenderness, and rebound tenderness were found at McBurney's point. The leucocyte count was elevated and a differential count showed a relative increase in polymorphonuclear neutrophils. A laparotomy was performed 18 hours after the initial symptoms. An acutely inflamed appendix with a small amount of serofibrinous exudate in the peritoneum was found. The appendix was removed and the wound closed without drainage.

Gross Examination.—The appendix measured 6 cm. in length and had a uniform diameter of 0.8 cm. The serosal surface of the distal half was covered by a thin film of fibrin. After the appendix was sectioned, there was noted no other macroscopic abnormality, and it appeared to be simply an acutely inflamed organ.

Histological Examination.—The appendix showed fibrous obliteration of the lumen near the distal end. The connective tissue was extensively infiltrated by polymorphonuclear neutrophils and lymphocytes. The muscularis and serosa also showed moderate polymorphonuclear neutrophilic and lymphocytic infiltration. In addition to the acute inflammatory exudate there were nests and cords of tumor cells invading the fibrous tissue replacing the lumen, and extending through the muscularis to the serosa (Fig. 1). These nests were composed of columnar to cuboidal cells which had round to oval, densely chromatic nuclei, and abundant, acidophilic cytoplasm. In the cytoplasm of many of these cells there were large mucoid globules, which gave a "signet-ring" appearance similar to that presented by the cells in a gastric carcinoma (Fig. 2). At one point invasion of a nerve by tumor cells was demonstrable. Mitotic figures were not seen. Examination of sections of the appendix proximal to the distal half failed to show any tumor tissue. The presence of mucus in the cells of this tumor supported the diagnosis of adenocarcinoma of the appendix because mucus is never seen in argentaffin tumors.

Fig. 1 (Case 1).—Nests of tumor cells infiltrating submucosa and muscularis of the obliterated portion of the appendix. Leucocytes of the accompanying acute inflammatory exudate also appear in the muscularis (masson trichrome stain x 90).

The morphologic resemblance of the tumor cells in the appendix to those of a gastric carcinoma prompted some observers to consider that the appendiceal tumor might have been a metastasis. Consequently, extensive x-ray examination of the gastrointestinal tract was performed, but no evidence of a primary tumor was found. Since the patient is alive and well 14 years after the operation, and free from any symptoms referable to the gastrointestinal tract, it seems most improbable that the tumor could have been a metastasis from a "clinically silent" gastric carcinoma.

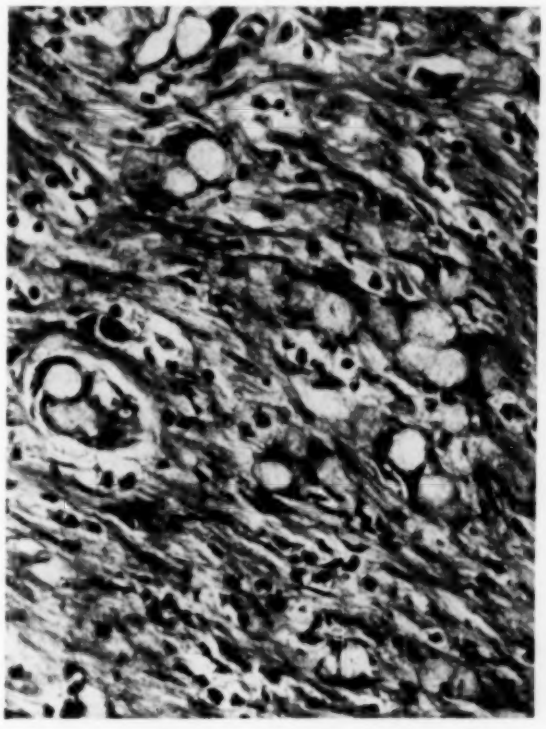


Fig. 2 (Case 1).— Nests of tumor cells in the muscularis showing signet-ring form produced by large globules of mucus in cell cytoplasm (Masson's trichrome stain x 395).

CASE 2.—An Indian woman aged 34, who had no previous complaints referable to the gastrointestinal tract, had right lower quadrant pain followed by nausea and vomiting. These symptoms persisted for three days. Physical examination showed localized pain, tenderness, and rebound tenderness at McBurney's point, and the leucocyte count was 18,200 with 85% neutrophils. A laparotomy was performed, and the appendix was removed. At the time the surgeon incised the appendix longitudinally for about half its length.

Gross Examination.—The appendix measured 9 cm. in length and 3 cm. in width. The mucosa was almost entirely replaced by a villous, but not ulcerated, tumor up to 1 cm. thick with small projecting finger-like processes. Grossly the mass appeared limited by the muscularis, but extended to the line of section at the base of the appendix and distended the lumen before it was opened.

Histological Examination.—The mucosa of the appendix was entirely replaced by tumor tissue composed of tall columnar cells arranged in layers varying from one to four cells deep supported by long delicate fibrous stalks (Fig. 3). The majority of these columnar cells contained cytoplasmic globules of mucus. The nuclei were round to oval in shape and contained many thin delicate strands of chromatin. They varied in their location from the base to the luminal margin of the cells. The cytoplasm was abundant and acidophilic. Scattered mitotic figures

were seen (Fig. 4). Although the majority of the cells of this tumor contained mucoid droplets, the cells were not signet-ring in type, but were of tall columnar goblet form as in the epithelium of the colonic mucosa. The muscularis mucosa was pressed down by the tumor and in turn condensed the submucosa, causing almost complete disappearance of areolar tissue. The basement membrane of the mucosa was thin, but there was no evidence of invasion by the tumor beyond this structure. The muscularis and serosa were infiltrated by a moderate number of polymorphonuclear neutrophils and lymphocytes, and a thin mat of fibrin and leucocytes covered the serosal surface.

The patient made an uneventful recovery from the operation and was discharged. Too short an interval of time has elapsed since the operation to determine whether the tumor will recur.

COMMENT

The structure of the tumors seen in these cases leaves little doubt as to the diagnosis of carcinoma of the mucus membrane type, apparently arising from the appendiceal mucosa. Like many of the earlier cases described, the structure is highly reminiscent of the common colonic malignant tumors.

The possibility that remnants of the tumor tissue might be found in the appendiceal stump and also that the condition might be a part of a multiple polyposis of the colon must be considered. From the information available in previously reported cases, it would seem that excision of a carcinomatous appendix is usually not followed by rapid recurrence of carcinoma and metastases, and that the cure rate is relatively high. The five patients of Uihlein and McDonald, for example, were alive at periods of 9 months, 1, 3½, 4, and 10 years after operation, while

Fig. 3 (Case 2).—Elaborate polypoid structure of tumor replacing the mucosa and compressing the submucosa on underlying muscularis (hematoxylin-eosin stain x 12).

those of Lesnick and Miller were alive at periods of 1, 2, 4, and 10 years. Of the patients described here, one is alive and well after 14 years, and the other was only recently discharged from the hospital.

Many of the reported cases initially presented the clinical signs and symptoms of an acute appendicitis; hence, carcinoma of the appendix must not be forgotten in the differential diagnosis of an acute abdominal crisis.

Fig. 4 (Case 2).—Glandular arrangement of tumor cells. Cells are tall columnar in form with occasional droplets of mucus in the supranuclear cytoplasm, and are arranged one to three layers deep. To the right a small secondary lumen appears in the gland. The stroma is delicate and infiltrated with lymphocytes (hematoxylin-eosin stain × 395).

SUMMARY AND CONCLUSIONS

The literature on primary carcinoma of the appendix is briefly reviewed, a record of 116 previously reported cases having been found. Two additional cases of primary carcinoma of the appendix are reported.

In spite of its morphologically malignant character, recurrence or metastasis of a primary carcinoma of the appendix appears to be at most a rare event and the prognosis is therefore good.

U. S. Public Health Service Hospital, New Orleans, La.

Hormones and Neoplasia.—A large gap exists in our knowledge of the relationship between hormone-induced tissue growth and the neoplastic process. It is equally clear that these two processes overlap sufficiently to demand the closest scrutiny of their possible interrelationships. Thus, the experimental production of malignancy by simple hormonal imbalance challenges the clinician to review the earlier medical history of patients with comparable malignancies in order to ascertain whether at any time they may have presented a picture of endocrine imbalance. In this way, the complete characterization of a premalignant state may become clear. Further, these manifestations of active humoral interrelationships serve to support the view that neoplasia is a local manifestation of a metabolic disorder. Thus, diagnostic and therapeutic efforts must be directed systemically as well as locally.—Roy Hertz, M.D., The Relationship Between Hormone-Induced Tissue Growth and Neoplasia, *Cancer*, June, 1951.

DIAPHRAGMATIC HERNIA WITH SEVERE ANEMIA AFTER TRANSABDOMINAL VAGOTOMY

Donald E. Van Hoek, M.D.
and
Merle M. Musselman, M.D., Eloise, Mich.

Diaphragmatic hernia, as a serious complication of abdominal vagotomy, has not been emphasized sufficiently. Neither Moses [1] nor Grimson and his associates [2] in their discussions of the complications of vagotomy, mention diaphragmatic hernia. Only two instances of this complication have been reported previously.[3] Anemia resulting from loss of blood from the herniated portion of the stomach is one reason for the seriousness of this complication. We are presenting a case in which a diaphragmatic hernia developed after an abdominal vagotomy. The patient was admitted to the hospital because of severe anemia, and was treated by partial gastrectomy and repair of the hernia.

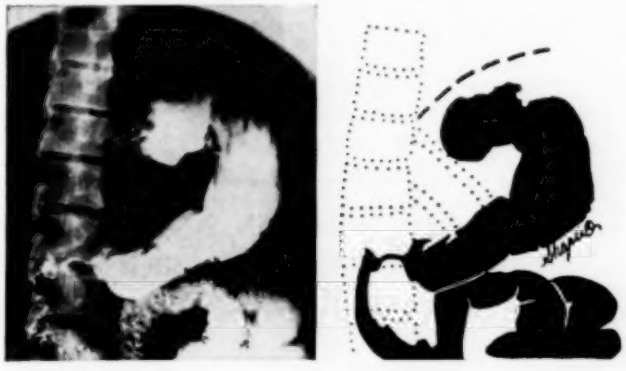


Fig. 1.—Print and line-drawing of roentgenogram taken prior to vagotomy. Contracted and deformed duodenal bulb with no definite ulcer crater and absence of hiatus hernia can be noted.

REPORT OF CASE

A woman aged 37 was admitted to Wayne County General Hospital on July 25, 1950, for severe secondary anemia. She complained of dizziness and weakness that had been present four months.

In 1948, the patient had entered another hospital with symptoms of duodenal ulcer. She had had four episodes of tarry stools. The hemoglobin level had been 12.5 gm. per 100 ml. of blood. Analysis of the gastric juice in the fasting state, prior to vagotomy, was reported as 44 clinical units of free acid and 53 clinical units of total acid. The x-ray findings were compatible with duodenal ulcer. The diaphragm was normal (Fig. 1). Transabdominal vagotomy was performed Sept. 2, 1948. The duodenum showed chronic scarring just distal to the pylorus. The peritoneum was incised at the esophageal hiatus, and the vagal trunks were sectioned. No attempt was made to repair the peritoneal defect. The postoperative course was uneventful. Following vagotomy, gastric analysis revealed 28 clinical units of free acid and 54 clinical units of total acid after histamine. Ten days after vagotomy the x-ray examination (Fig. 2) revealed no evidence of diaphragmatic hernia. A diaphragmatic hernia (Fig. 3) was first demonstrated four months after the operation.

On admittance to Wayne County General Hospital the patient was anemic and obese, but otherwise normal by physical examination. The hemoglobin level was 6 gm. per 100 ml. of blood, and the red blood cell count was 2,740,000. Gastric analysis showed 34 clinical units of free acid and 46 clinical units of total acid after histamine. The Hollander test showed 102 clinical units of free acid and 110 clinical units of total acid. Examination of the feces revealed 4+ occult blood on four occasions. A diaphragmatic hernia with approximately one-third of the stomach herniated into the posterior mediastinum (Fig. 4) was demonstrated by x-ray examination. The esophagus was of normal length. A deformity of the duodenal bulb was interpreted as being the result of an old duodenal ulcer.

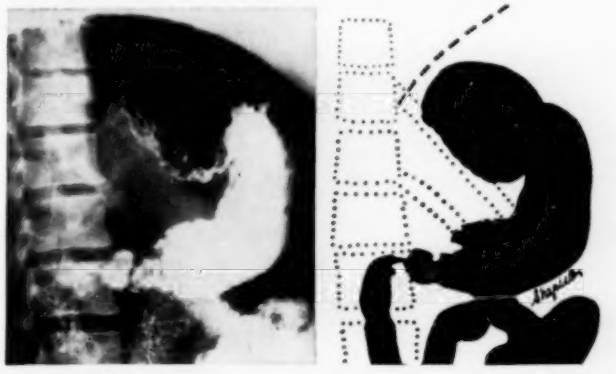


Fig. 2.—Print and line drawing of roentgenogram taken 10 days after vagotomy. The deformed, irritable duodenal bulb with no definite ulcer crater and absence of hiatus hernia can be noted.

After a month of observation, treatment on an ulcer diet, and multiple blood transfusions, on Aug. 31, 1950, a subtotal gastric resection and repair of the hernia were performed through an upper abdominal transverse incision. This operative plan was chosen because we were not certain whether the severe anemia resulted from loss of blood consequent to the diaphragmatic hernia, or from a reactivated duodenal ulcer.

At operation, chronic scarring of the duodenum was noted again. Approximately one-third of the stomach was herniated through the esophageal hiatus into the mediastinum, and the wall of the stomach was adherent to the mediastinal tissue. No gross ulceration of the stomach was demonstrated.

The postoperative course was uneventful except for moderate symptoms of gastric atonia. X-ray examination on Sept. 14, 1950, revealed no evidence of diaphragmatic hernia, and the gastrojejunostomy was functioning normally (Fig. 5). The patient was discharged on the 16th postoperative day.

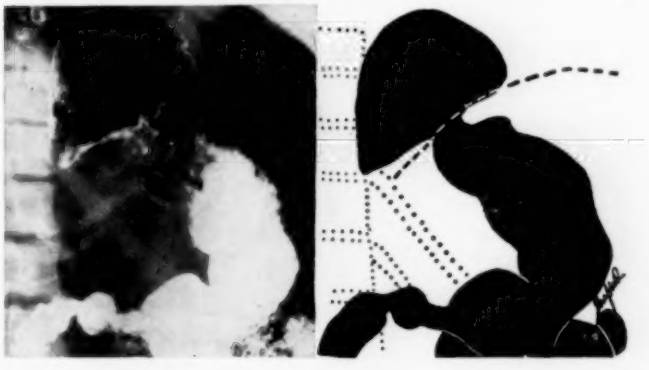


Fig. 3.—Print and line drawing of roentgenogram taken four months after vagotomy. Large hiatus hernia can be noted. Duodenal bulb is slightly irritable with no marked deformity or definite ulcer crater.

The patient was observed for three and one-half months after the operation. She had no symptoms referable to the chest or abdomen. A normal level of hemoglobin had been maintained, and no gross or occult blood was found in the stool.

From the Department of Surgery, Wayne County General Hospital.

1. Moses, W. R.: Critique on Vagotomy, New England J. Med. **23**: 603 (Oct. 23) 1947.

2. Grimson, K. S.; Rundles, R. W.; Baylin, G. J.; Taylor, H. M., and Linberg, E. J.: Vagotomy: Observations During 4 Years, Surgery **27**: 49 (Jan.) 1950.

3. (*a*) Beal, J. M.: Diaphragmatic Hernia Following Subdiaphragmatic Vagotomy, Surgery **24**: 625 (Oct.) 1948. (*b*) Hanlon, C. R., and Higgins, R. P., Jr.: Diaphragmatic Hernia Following Subdiaphragmatic Vagotomy and Partial Gastrectomy, Surgery **27**: 460 (March) 1950.

COMMENT

The severe anemia in the above patient represents a possible serious sequel of diaphragmatic hernia complicating abdominal vagotomy. This type of traumatic hernia has grave potentialities. Since the hernia has no sac, the tissues become adherent and incarceration is

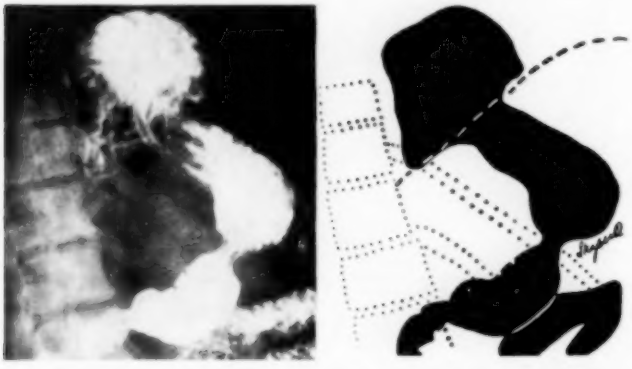


Fig. 4.—Print and line drawing of roentgenogram taken two years after vagotomy. Large hiatus hernia and deformity of duodenal bulb with no definite ulcer crater can be noted.

likely to occur. Strangulation and obstruction are prone to develop because of the narrow firm margin of the defect. Contraction or spasm of the diaphragm enhances this possibility. The patient of Hanlon and Higgins [3b] required operation because of bowel obstruction; several loops of small intestine and a loop of transverse colon were incarcerated in the hernia. Beal's [3a] patient likewise required repair of the hernia, although the reasons for the operation were not given. A transthoracic approach was used in both of these cases.

The patient discussed in this report was suffering from severe loss of blood from the upper gastrointestinal tract. Schwartz [4] reported 20 instances of severe anemia from chronic loss of blood secondary to diaphragmatic hernia. Of 46 subjects with diaphragmatic hernia seen at Wayne County General Hospital between 1939 and 1949, thirty-six had no other disease process which could

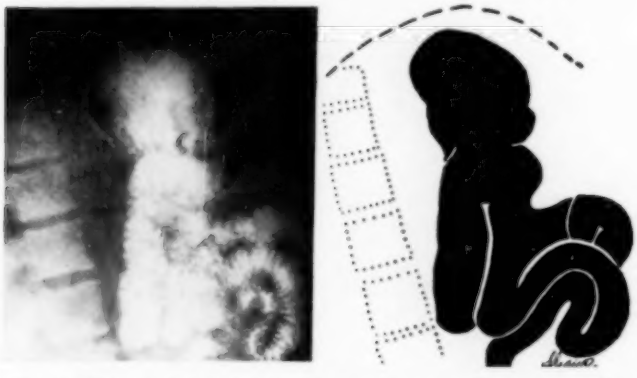


Fig. 5.—Print and line drawing of roentgenogram taken two months after partial gastrectomy and repair of hiatus hernia. Functioning gastrojejunostomy can be noted. There is no recurrence of hiatus hernia.

account for anemia or melena. Of these 36 patients, 17 (47%) had moderate to severe anemia. Among the 36 patients, the stools were examined for blood in 21; in 12 of the 21 (57%) occult blood was found. All these patients had true hernias with a peritoneal sac. A higher incidence of bleeding may be expected in traumatic hiatus hernias, in which incarceration is common, because bleeding occurs most frequently in such hernias when incarcerated.

The site of bleeding in our patient could not be determined definitely. Therefore, we elected to carry out both a partial gastric resection and a repair of the hernia. The operation was performed by the abdominal approach.

We believe that diaphragmatic hernia can be prevented by repairing the peritoneal defect at the time of vagotomy. Beal [3a] and Hanlon and Higgins [3b] emphasized the importance of closing the mediastinal defect made for exposure of the vagus trunks, as recommended by Dragstedt and his associates.[5] The experience of Hanlon and Higgins indicates that transabdominal vagotomy with concomitant partial gastrectomy confers no protection against the development of diaphragmatic hernia.

SUMMARY

Diaphragmatic hernia is a serious but avoidable complication of transabdominal vagotomy. Hemorrhage as well as incarceration, obstruction, and strangulation of the involved viscera may be expected in such diaphragmatic hernias. Operative correction generally is to be recommended.

4. Schwartz, S. O.: Severe Anemia Secondary to Diaphragmatic Hiatus Hernia: Report of 20 Cases, Illinois M. J. **97**: 204 (April) 1950.

5. Dragstedt, L. R.; Fournier, H. J.; Woodward, E. R.; Tovee, E. B., and Harper, P. V.: Transabdominal Gastric Vagotomy, Surg., Gynec. & Obst. **85**: 461 (Oct.) 1947.

COUNCIL ON NATIONAL EMERGENCY MEDICAL SERVICE

This paper is one of a series requested by the Council on National Emergency Medical Service to inform the medical profession on problems pertaining to civil defense. It does not necessarily reflect, however, the opinions of the Council or of any other official body unless so stated in the article.

C. JOSEPH STETLER, *Secretary.*

NATURE OF AIR RAID CASUALTIES

Cortez F. Enloe Jr., M.D., New York

If we are bombed tomorrow, any type of protection that can be given to the individual will be better than none at all. But this premise, if continually accepted, is not planning. It is improvisation, and poor improvisation at that. What is required is medical planning, for that is the only sensible manner in which our profession can discharge the new and staggeringly tremendous obligation, quietly and almost imperceptibly being thrust on us by the new fact of life, civil defense. For physicians to be disinterested in this new aspect of their professional and private lives, for them to fail to see the immensity of the problem faced by the physicians of the United States, will be to evade responsibility at a time —should atomic attack come—when the survival of our

The notes of Dr. Franz K. Bauer of Los Angeles were referred to in the preparation of this paper.

Dr. Enloe was Chief of the Medical Science Branch, United States Strategic Bombing Survey. This survey of bombing effects on German health and medical care was conducted by civilian and military personnel at the direction of the President of the United States. Dr. Enloe was recently awarded the Legion of Merit for his work in this capacity.

country will depend upon the American medical profession more than upon any other group of our citizens.

Civil defense medical care may be divided into three phases: what physicians can do before an atomic attack; during the attack, and after the attack. The period of rehabilitation, or the third phase of medical care, is well understood; the techniques of medical practice in peacetime are readily adaptable to those required after air raids on our cities. What physicians should do in the period of emergency when the country is under attack has been precisely outlined by the previous authors in this series of reports. What the profession can accomplish in peace time, the first phase of civil defense medical care, can be best understood from a description of the nature of the casualties that may occur.

This report is not primarily concerned with the types of injuries peculiar to the atomic blast, such as radiation injuries, as those do not constitute the major medical problem of civil defense. Casualties resulting from atomic blast are dealt with elsewhere in this series, and the types of injuries in themselves suggest the precautions which must be taken by medical authorities. What we are concerned with here are the injuries that will constitute from 70 to 80% of all of the casualties that may be expected in a heavy attack on an American city.

A careful scrutiny of the types of casualties experienced in the high explosive and fire-bomb raids on German cities and comparison with those that occurred in the atomic bomb raids on Hiroshima and Nagasaki afford conclusive evidence that there is little difference in the types of injuries sustained by the individual. Excluding radiation effects, which may be expected to account for approximately 20% of the total casualties, the remainder of the casualties may be classified as follows:

1. External injury resulting from
   (*a*) burial under rubble and debris
   (*b*) objects flying at extreme velocity
   (*c*) explosions, immersion, scalding, chemical burns, poisoning and by-products of exploded bombs
   (*d*) fire (direct contact)
   (*e*) lack of proper serological prophylaxis
2. Internal injury resulting from
   (*a*) carbon monoxide inhalation in air raid shelters (occasionally occurring during rescue work)
   (*b*) effect of heat through conduction and thermal radiation of extremely high temperatures
   (*c*) overheating for a long period, at temperatures that can be tolerated normally for a short time only
   (*d*) dust inhalations, blocking of the upper respiratory passages, with damage to the small bronchi and alveoli
   (*e*) psychosomatic collapse in the critically ill
   (*f*) blast injuries in which internal injuries may or may not be masked by external trauma.

EXTERNAL INJURIES

Mechanical Injuries.—Injury and death from mechanical causes head the list of casualties. Direct hits by flying debris, burial under rubble from collapsed buildings, and burns, all conditions which the physician will recognize as being closely associated with shock, may be expected to form the principal category of injuries. Even a moderately substantial shelter will protect a person from such bomb effects.

Thermal Injuries.—For those sheltered from such mechanical injuries, however, there remains the greater peril, fire. In many respects, the atomic bomb is a tremendous incendiary. Although blast is responsible for most of the destruction caused by an atomic bomb, the Atomic Energy Commission has stated that "thermal radiation can make a significant contribution to the total damage by producing skin burns in living organism and, to a lesser extent, by igniting combustible structures and initiating fires." Whereas in a high-explosive raid (the type carried out on European cities and the type to which this country is apparently almost immune) mechanical injuries would outnumber deaths, in an atomic bomb attack, it is expected that the effects of heat and carbon monoxide would cause more deaths than injuries. The crowded conditions of American cities, the height of buildings, the age of dwellings, the type of construction —all these are factors that would influence the spread of fire following an atomic attack.

The experience of protecting people from a fire in peacetime provides little preparation for what happens in the type of fires that follow atomic bombing. In the first place, in peacetime fires occur singly. There is very little danger of persons being buried in the rubble. There is almost no problem of superheated air, and there is not the great chaos that occurs when an entire area of a city is in flames. This difference becomes dramatically apparent when one reflects that in a peacetime fire the family is usually standing across the street watching their belongings being thrown out of the window, whereas in an atomic conflagration they are sealed in the cellar to which they have retreated.

Fig. 1.—Occupant of air raid shelter found several days after raid. Death apparently came without struggle.

To reduce the number of casualties in an air raid, it is essential that the medical profession give thought to the protection of people from the effects of heat, including the effect of intense heat of short duration from conduction or thermal radiation, with the production of burns, and the effects of high temperature over long periods. The latter may not result in skin damage, but it usually causes the same syndrome as heat stroke.

INTERNAL INJURIES

Heat Stroke.—The time at which injury from heat occurs varies with several factors, such as the humidity of the air, the cessation of sweat production, and the degree and duration of heat to which the body has been exposed. In humid air, heat stroke may occur in a tem-

perature of 60 C and not necessarily be associated with subjective complaints. This factor accounted for the many persons found dead in rooms from which escape would have been possible and found in a position not suggestive of agony before death (Fig. 1).

Effects of Intense Heat.—One of the fire raids on which we have the most complete data was made on Hamburg, Germany, in the summer of 1943. It is well to remember that during this raid 60,000 inhabitants of this city were killed, almost as many as were killed in the atomic bomb raid on Hiroshima. Police engineers in Hamburg estimated that temperatures in the burning city blocks went as high as 800 C (1472 F). Hundreds of persons were seen leaving shelters after the heat became unbearable. They ran into the streets and were seen to collapse very slowly, as if from utter exhaustion. Many thus felled were found naked (Fig. 2). Two explanations have been offered for this phenomenon: The first is that flames spurted across the avenue with the speed of a tornado and consumed the victim's clothing, singeing the skin; the other is that the intense heat disintegrated the clothes without actual burning. Shoes were usually the only covering left on the bodies. When the bodies were recovered, they were not burned to ashes, but the body tissue was dry and shrunken and resembled that of a mummy. In many cases, the intense heat caused the skin to burst and retract over the elbows, the scalp, and the orbit (Fig. 3). Autopsies performed on a large number of these bodies showed venous stasis with increased permeability of the small blood vessels,

Fig. 2.—Man killed by intense heat in the street while running to safety. Clothes were incinerated while shoes are intact. Position suggests effort to raise himself and keep going.

as well as damage to the chromatin and to practically all the cells of the abdominal organs and the lungs. This result has been attributed to the inhalation of superheated air.

Beyond the local effects of heat, overburdening of the heat-regulating mechanism of the body must also be considered. Hindrance of the heat exchange between the body and the external atmosphere may be the causative factor. Many air raid shelters closed off by rubble produced an atmosphere intolerable to the occupants. Heat damage was noted in members of rescue squads who entered basement shelters where proper ventilation had been cut off for some time (Fig. 4 and 5). Escape from

Fig. 3.—Victim of heat. Position of hair clearly shows splitting and retraction of scalp and skin around orbits. Clothing practically intact.

overheated shelters has its hazards, too. In escaping through burning city blocks the danger is chiefly from radiated heat. The inhalation of hot air may cause severe damage to the respiratory passages, such as ulcerous necrosis of the mucous membranes. Whether this is a separate entity or part of the whole picture of injury and death is as yet undetermined.

Carbon Monoxide Poisoning.—It should be kept in mind that any inhalation of dangerous gases or by-products of fire must also be considered. Carbon monoxide poisoning is one of the chief types of injuries that the physician may expect to encounter. It is the characteristic cause of injury and death from the air in public air raid shelters, and improvised home shelters. Carbon monoxide casualties may always be expected in flaming buildings where exits have been blocked by rubble, indicating the imperative need for adequate exits. One cannot glibly endorse the general attitude that the basement of every dwelling affords relative safety. It may afford safety from blast, but if the building catches fire and, as we have said, fire is the main cause of atomic bomb damage, the cellar becomes but a tomb. It is interesting to note that in one fire raid on the city of Wesermünde, 175 out of 210 corpses recovered presented a picture of acute carbon monoxide poisoning. In Hamburg, it has been conservatively estimated that 70% of all casualties not resulting from mechanical injury or burns were induced by carbon monoxide.

A concentration of 0.5% carbon monoxide in the air may cause death after one hour's exposure. A concentration of even 0.1% may still produce symptoms of intoxication. Thus, when it is realized that the fumes from ordinary fires are said to contain 3% carbon monoxide, coal gas 6%, and gas from high explosive bombs

60 or 70%, it is not strange that carbon monoxide poisoning must be considered a prime cause of death and injury. Characteristic of carbon monoxide deaths in air raid shelters were the peaceful positions of the bodies found in one shelter, positions suggestive of complete lack of apprehension of imminent danger. Recognition of the importance of carbon monoxide poisoning indicates the urgent need for laboratory and clinical research on the prevention and treatment of carbon monoxide intoxication.

Air Blast Injuries.—Injury from air blast itself, as distinguished from injury caused by fragments carried by the blast, may be expected to be encountered relatively infrequently. It will affect only those people who are in the open at the time the bomb explodes. However, the intensity of an atomic bomb explosion is so great that persons close enough to be damaged by the air blast will probably also be consumed by the ball of fire that will extend beyond the critical area where the blast itself can cause physical damage to a human being. Some such blast injury may be experienced by persons trapped in hallways, or near the entrance to open manholes or other man-made caves from which the blast wave cannot escape. In such instances, the pressure wave is compressed and may be expected to result in injuries to the ear, such as perforated drum membranes, damage to

Fig. 4.—Effect of dry heat in a group of occupants of an air raid shelter. Note splitting of scalp and skin around orbits. Clothing is practically intact.

Corti's organs, and inner ear deafness, and also cause tearing of lung tissue, resulting in air embolism, and conjunctival and retinal hemorrhages. Shielding of any kind in these circumstances will afford a great measure of protection from air blast.

Blockage of the Upper Respiratory Passages.—The inhalation of dust is seldom a cause of death, yet it is a casualty-producing factor which the physician must take into consideration. After air raids, there have been some cases in which the patient's upper respiratory passages down through the larynx were blocked with dust. Strangely, only small amounts of dust were found in the alveoli in such patients. Therefore, it is held that the

Fig. 5.—Shelter occupant in advanced state of cremation by dry heat.

inhalation of extremely dense concentrations of dust does not interfere with the gas exchange in the alveoli but results in a physical blockage of the air passages. The afflicted persons literally "drown in dust."

Drowning.—In considering the health and safety aspects of air raid shelters, the physician should not overlook the possibility of death by immersion. The breaking of water mains as a result of the blast of an atomic bomb and the collapse of buildings, would permit water to seep into shelters and basements, drowning the occupants.

Hysteria.—Contrary to expectations, it has not been demonstrated that air attacks on civilian population increase the incidence of psychiatric disorders. There is no evidence to support an occasionally voiced prognostication that either organic-neurologic diseases or psychiatric disorders can be attributed to, or even conditioned by, air attacks. To be sure, the physician must anticipate some fleeting reaction symptoms in the nature of neurohysteria after a severely damaging attack, but that these may be of an enduring and psychotic nature is dubious, and has not been proved by experience thus far. Air raids may slightly influence the course of affective emotional disorders and increase tension states, anxieties, and exhaustive states among the people, but this may not be expected to occur to an alarming degree. It is questionable, therefore, whether such protective measures as the establishment of psychiatric first-aid stations are necessary. As a hypothesis, it appears sound, but experience has shown that it is a waste of time.

CONCLUSION

The foregoing suggests the type of air raid casualties which the civilian physician may expect. It is our duty and responsibility to take such measures as we can to reduce the incidence of such appalling injuries. Civil defense is here to stay. It is now a fact in our lives; it is not transient but permanent, and the medical profession stands first in the line of those who can reduce the effect of enemy attacks on our countrymen. Our job is not only to treat the wounded and to rehabilitate them so that the country can carry on but also to ferret out those places in our communities where our scientific knowledge and professional guidance can lead to increased protection of the individual in order that fewer will need treatment when catastrophe descends upon us.

Suite 5130, 500 Fifth Ave.

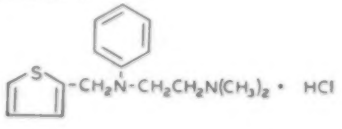
COUNCIL ON PHARMACY AND CHEMISTRY

NEW AND NONOFFICIAL REMEDIES

The following additional articles have been accepted as conforming to the rules of the Council on Pharmacy and Chemistry of the American Medical Association for admission to New and Nonofficial Remedies. A copy of the rules on which the Council bases its action will be sent on application.

R. T. STORMONT, M.D., *Secretary.*

Methaphenilene Hydrochloride.—Diatrine Hydrochloride (Warner). — N,N-Dimethyl-N′-(α-thenyl)-N′-phenylethylenediamine hydrochloride.—$C_{15}H_{20}N_2S.HCl$.—M.W. 296.86.—The structural formula for methaphenilene hydrochloride may be represented as follows:



Actions and Uses.—See general statement on Histamine-Antagonizing Agents. Methaphenilene hydrochloride is therapeutically effective and induces low incidence of side reactions. It has a moderate tendency to cause gastrointestinal irritation.

Dosage.—The average adult dose is 50 mg. As with other antihistaminic drugs, the dose used should be the smallest which will relieve symptoms.

Tests and Standards.—

Physical Properties: Methaphenilene hydrochloride occurs as a white to pale yellow, crystalline powder, having a faint odor. It melts between 184 and 189 C. It is soluble in water, sparingly soluble in alcohol and chloroform, and practically insoluble in ether. The free base is obtained as an oil on the addition of sodium hydroxide T.S. to an aqueous solution of methaphenilene hydrochloride. A 2% aqueous solution of methaphenilene hydrochloride has a pH between 4.8 and 5.6.

Identity Tests: Add about 50 mg. of methaphenilene hydrochloride to 2 cc. of sulfuric acid: a pale yellow solution is obtained which becomes a light orange upon standing. Add 2 drops of a 1% solution of isatin in sulfuric acid to the solution of methaphenilene in sulfuric acid: a deep cherry-red color develops within one minute.

Add 3 drops of a saturated aqueous solution of Reinecke's salt to 2 cc. of a 2% aqueous solution of methaphenilene hydrochloride: a pink precipitate is formed.

Dissolve about 25 mg. of methaphenilene hydrochloride in 5 cc. of water. Add a few drops of diluted nitric acid, followed by 1 cc. of silver nitrate T.S.: a white precipitate of silver chloride is obtained.

Purity Test: Dissolve 1 gm. of methaphenilene hydrochloride in 25 cc. of water. Add 1 cc. of diluted hydrochloric acid and then add 10 cc. of hydrogen sulfide T.S. The color produced is less than that obtained when 2 cc. of standard lead solution (*U. S. P. XIV*) is treated in a similar manner (*heavy metals*).

Dry about 1 gm. of methaphenilene hydrochloride, accurately weighed, at 110 C. for 4 hours: the loss in weight does not exceed 0.5%.

Char about 0.5 gm. of methaphenilene hydrochloride, accurately weighed, over a low flame. Cool, then add 1 cc. of sulfuric acid and continue ignition until no carbon remains: the residue should not exceed 0.15%.

Assay: (Methaphenilene Hydrochloride) Transfer 0.1 gm. of methaphenilene hydrochloride, accurately weighed, to a 100 cc. volumetric flask and dilute to the mark with alcohol. Mix thoroughly and transfer 10 cc. of the solution to another 100 cc. volumetric flask. Dilute to 100 cc. with alcohol; mix well and transfer 10 cc. of the solution to a third 100 cc. volumetric flask and dilute to 100 cc. The final solution (0.001%) exhibits ultraviolet absorption maxima at 2,450 A. [specific absorbancy, E (1%, 1 cm.) = 537 ± 5] and 2,900 A., and a minimum at 2,840 A.

Transfer about 0.2 gm. of methaphenilene hydrochloride, accurately weighed, to a 100 cc. volumetric flask and fill to the mark with water. With constant stirring, add, dropwise, from a burette, exactly 50 cc. of the solution to 25 cc. of a saturated aqueous solution of picric acid containing 0.2 cc. of sulfuric acid. Allow the precipitated dipicrate to digest at room temperature for 2 hours, with occasional stirring. Cool to 0 C. in an ice-bath and filter quantitatively into a tared sintered glass crucible, using the filtrate to effect complete transfer of the precipitate. Wash carefully with five 1 cc. portions of water cooled to 0 C. Dry in a vacuum desiccator over phosphorus pentoxide at room temperature to a constant weight—this takes about four hours. Each gram of methaphenilene dipicrate is equivalent to 0.4131 gm. of methaphenilene hydrochloride. The amount of methaphenilene hydrochloride is not less than 98 nor more than 102%. The yellow methaphenilene dipicrate melts (*caution!*) between 130 and 135 C.

(Nitrogen) Transfer 0.1 gm. of dry methaphenilene hydrochloride, accurately weighed, to a semi-micro Kjeldahl flask and digest it with 5 cc. of sulfuric acid, 2 gm. of potassium sulfate, 0.2 gm. of cupric sulfate and 1 cc. of 30% hydrogen peroxide. With water dilute the clear solution to 15 cc., make it alkaline with 40% sodium hydroxide, and distil the ammonia into 50 cc. of 0.02 *N* sulfuric acid. Titrate the excess acid with 0.02 *N* sodium hydroxide, using methyl red T.S. as an indicator. The amount of nitrogen present is not less than 9.2 nor more than 9.6%.

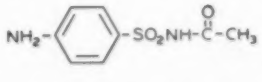
(Chloride) Transfer about 0.5 gm. of dry methaphenilene hydrochloride, accurately weighed, to a 100 cc. volumetric flask. Add 50 cc. of water and 10 cc. of diluted nitric acid. Mix thoroughly and add exactly 25 cc. of 0.1 *N* silver nitrate, and fill to the mark with distilled water. Shake the mixture vigorously and allow the silver chloride to settle out. Transfer exactly 50 cc. of the clear, supernatant liquid into a flask and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate, using ferric ammonium sulfate T.S. as an indicator. Each cc. of 0.1 *N* silver nitrate is equivalent to 0.02969 gm. of methaphenilene hydrochloride. The amount of methaphenilene hydrochloride found is not less than 99 nor more than 101%.

Dosage Forms of Methaphenilene Hydrochloride

TABLETS: Methaphenilene hydrochloride tablets respond to the identity tests and assays described in the monograph on methaphenilene hydrochloride. They contain not less than 95 nor more than 105% of the labeled amount.

Tablets Diatrine Hydrochloride: 50 mg. U. S. Trademark 506,769. U. S. Patent 2,526,943. Wm. R. Warner & Company, Inc., New York.

Sulfacetamide.—Sulamyd (Schering).—$C_8H_{10}N_2O_3S$.—M.W. 214.24.—N-Sulfanilylacetamide.—N^1-Acetylsulfanilamide.—The structural formula of sulfacetamide may be represented as follows:



Actions and Uses.—See general statement on Sulfonamides (New and Nonofficial Remedies 1951).

It possesses the advantage of greater solubility in the urine than the pyrimidine derivatives and therefore has less tendency to produce concretions in the urinary tract.

Dosage.—Adults, 1 gm. of sulfacetamide three times daily after meals; children 0.06 gm. per kilogram of body weight daily (approximately 0.5 gm. per 15 lb.) in three equally divided doses after meals. The drug should be continued for at least a week after all symptoms have disappeared. If no improvement occurs after 10 days of treatment, the drug usually can be considered to have failed in its purpose. For prophylactic use, 0.5 gm. three times daily after meals is recommended for 24 hours prior to and 48 hours after manipulative or surgical procedures on the genitourinary tract.

Blood levels should be determined during administration of the drug. In cases of impaired kidney function with above average blood concentration and, in any case, when the blood level exceeds 12 mg. % of free sulfacetimide, the drug should be discontinued and fluids forced.

Tests and Standards.—

Physical Properties: Sulfacetamide is an odorless, white, crystalline powder with a characteristic sour taste. One part of sulfacetamide is soluble in about 140 parts of water. It is freely soluble in dilute mineral acids and aqueous solutions of potassium hydroxide and sodium hydroxide, soluble in alcohol, slightly soluble in ether, very slightly soluble in chloroform and practically insoluble in benzene. It melts between 181 and 184°, and decomposes with the evolution of gas between 190 and 195°. Aqueous solutions are stable only in the pH range of 7 to 9, and are sensitive to light.

Identity Tests: Place about 0.5 gm. of sulfacetamide in a test tube and heat gently until a boiling action takes place. An oily liquid condenses on the walls of the test tube: this liquid has the characteristic odor of acetamide *(distinction from the sublimates of sulfadiazine, sulfamerazine, sulfamethazine and sulfapyrazine, which are solids at room temperature).*

To about 0.1 gm. of sulfacetamide add 5 ml. of water and just enough sodium hydroxide T.S. to dissolve the powder. Add 5 drops of cupric sulfate T.S.: a light bluish green precipitate forms, which remains unchanged on standing *(distinction from sulfanilamide, which forms no precipitate or a light blue one; from sulfadiazine, which forms an olive-green precipitate, changing to purple-gray on standing; from sulfaguanidine, which is insoluble in cold sodium hydroxide, but gives a dark brown precipitate in boiling solutions; from sulfamerazine, which forms an olive-green precipitate, changing to dark gray on standing; from sulfamethazine, which forms a yellow-green precipitate, changing to brown on standing; from sulfapyrazine, which forms a light green precipitate, changing to white on standing; from sulfapyridine, which forms an apple-green precipitate, changing to olive-green on standing; and from sulfathiazole, which very rapidly changes from a brown to a violet precipitate).*

Purity Tests: Dissolve about 0.2 gm. of sulfacetamide in 5 ml. of sodium hydroxide T.S.: the solution is yellow to faintly yellow without more than a trace of turbidity.

Dissolve 0.5 gm. of sulfacetamide in a mixture of 5 ml. of hydrochloric acid and 5 ml. of water, add 1 ml. of barium chloride T.S., mix well and allow to stand for 10 minutes: the turbidity does not exceed that of a control containing 0.2 ml. of 0.02 *N* sulfuric acid *(presence of sulfates).*

Dissolve 1 gm. of sulfacetamide in just enough sodium hydroxide T.S. to give complete solution, and add 20 ml. of water and 5 drops of freshly prepared sodium sulfide T.S.: the turbidity developed does not exceed that of a control containing 20γ of lead *(U. S. P. XIV,* p. 717).

Dry about 1 gm. of sulfacetamide, accurately weighed, at 105° for 4 hours: the loss in weight is not more than 0.5%.

Ignite about 1 gm. of sulfacetamide, accurately weighed. Cool, add sufficient sulfuric acid to moisten the charred mass and ignite to constant weight: the ash is not more than 0.1%.

Assay: (Sulfacetamide) Transfer about 0.5 gm. of sulfacetamide, accurately weighed, to a 250 ml. beaker. Proceed as described in the assay in the monograph for Sulfadiazine in *U. S. P. XIV,* p. 577. Each milliliter of 0.1 M sodium nitrite is equivalent to 0.02142 gm. of sulfacetamide. The amount of sulfacetamide present is not less than 99.0 nor more than 101.0%.

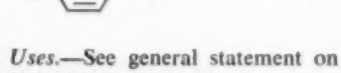
Dosage Forms of Sulfacetamide

TABLETS. *Identity Tests:* Grind enough tablets to contain 2.5 gm. of sulfacetamide into a fine powder. Reflux the powder with 50 ml. of acetone for 10 min., filter the mixture and evaporate the filtrate to dryness on a water bath. The residue responds to the identity tests in the monograph for Sulfacetamide.

Assay: (Sulfacetamide) Accurately weigh 20 or more tablets, grind them to a fine powder and accurately weigh an amount of powder equivalent to about 0.5 gm. of sulfacetamide. Proceed as described in the assay in the monograph for Sulfacetamide. The amount of sulfacetamide present is not less than 95.0 nor more than 105.0% of the labeled amount.

Tablets Sulamyd: 0.5 gm. U. S. Patent 2,411,495. U. S. Trademark 379,386. Schering Corporation, Bloomfield, N. J.

Sodium Sulfacetamide.—Sodium Sulamyd (Schering).—$C_8H_9N_2NaO_3S.H_2O$.—M.W. 254.25.—The monohydrated sodium salt of N-sulfanilylacetamide.—The structural formula may be represented as follows:



Actions and Uses.—See general statement on Sulfonamides (New and Nonofficial Remedies 1951).

The sodium salt is highly soluble at the physiologic pH of 7.4; therefore, it is especially suited, as a solution, for repeated topical application in the local management of ophthalmic infections susceptible to sulfonamide therapy.

Dosage.—Sodium sulfacetamide is topically applied to the eye as a 30% solution or as a 10% ointment. The ointment should not be employed in the presence of penetrating wounds of the cornea and is ordinarily reserved for night time application as an adjunct to the use of the solution during the day. Prophylactic instillation of one drop of a 30% solution, four to six times daily is recommended for two days following the epithelization of lesions resulting from corneal abrasions, lacerations, burns, or the removal of a foreign body. In acute infections, one drop every two hours, or less frequently, is used during the day according to severity; in chronic infections, one drop three times daily is considered adequate. At bedtime, application of a small amount of a 10% ointment to the lower lid is recommended.

Tests and Standards.—

Physical Properties: Sodium sulfacetamide is a white, odorless, bitter, crystalline powder. One part of sodium sulfacetamide is soluble in 2.5 parts of water. It is sparingly soluble in alcohol; and practically insoluble in benzene, chloroform and ether. The pH of a 5% solution is between 8.0 and 9.5. Aqueous solutions of sulfacetamide sodium must be refrigerated and protected from light.

Identity Tests: Dissolve about 4 gm of sodium sulfacetamide in 200 ml. of water, add 20 ml. of acetic acid and filter. Save the filtrate. Wash the residue with water and dry it overnight at 105°. The dried powder responds to the physical properties, identity tests and assay in the monograph for Sulfacetamide.

The filtrate from the precipitation of sodium sulfacetamide, above, responds to the tests for sodium in *U. S. P. XIV,* p. 724.

Purity Test: Dissolve 0.5 gm. of sodium sulfacetamide in a mixture of 5 ml. of hydrochloric acid and 5 ml. of water, add 1 ml. of barium chloride T.S., mix well and allow to stand for 10 min.: the turbidity does not exceed that produced in a control containing 0.2 ml. of 0.02 *N* sulfuric acid *(presence of sulfates).*

Dissolve 1 gm. of sulfacetamide sodium in 20 ml. of water and add 5 drops of freshly prepared sodium sulfide T.S.: the turbidity developed does not exceed that developed in a control containing 20γ of lead *(U. S. P. XIV,* p. 717).

Dry about 0.1 gm. of sodium sulfacetamide, accurately weighed, at 105° for 12 hours: the loss in weight is not less than 6.9 nor more than 7.3%.

Assay: (Sulfacetamide) Transfer about 0.5 gm. of sodium sulfacetamide, accurately weighed, to a 250 ml. beaker. Proceed as described in the assay in the monograph for Sulfadiazine, *U. S. P. XIV,* p. 577. Each milliliter of 0.1 M sodium nitrite is equivalent to 0.02142 gm. of sulfacetamide and to 0.02543 gm. of sodium sulfacetamide. The amount of sodium sulfacetamide present is not less than 99.0 nor more than 101.0%.

Dosage Forms of Sodium Sulfacetamide

OINTMENT. *Identity Tests:* Place an amount of ointment containing about 1 gm. of sodium sulfacetamide in a 60 ml. separatory funnel and add 10 ml. of water. Place the funnel in a steam bath until the temperature of the mixture is about 60°. Shake it for about 2 minutes and replace it in the steam bath for the layers to separate. Draw off the aqueous layer and centrifuge to clarify it. Make it up to about 200 ml. with water. Add enough hydrochloric acid to lower the pH to between 4 and 5, and filter. Proceed as described under identity tests in the monograph for Sodium Sulfacetamide starting with, "Wash the residue with water . . ."

Assay: (Sulfacetamide) Accurately weigh into a tared 125 ml. separatory funnel an amount of ointment containing about 0.5 gm. of sodium sulfacetamide. Extract it six times with 25 ml. portions of hot water, keeping the funnel in a steam bath while the layers are separating. Combine the aqueous extracts and proceed as directed in the assay for sulfadiazine, *U. S. P. XIV,* p. 578, starting with, "Add 20 cc. of hydrochloric acid . . ." Each milliliter of 0.1 M sodium nitrite is equivalent to 0.02142 gm. of sulfacetamide and to 0.02543 gm. of sodium sulfacetamide. The amount of sulfacetamide present is not less than 80.0 nor more than 88.4%, equivalent to not less than 95.0 nor more than 105.0% of the labeled amount of sodium sulfacetamide.

SOLUTION. *Identity Tests:* Accurately measure an amount of solution equivalent to about 4 gm. of sodium sulfacetamide into a 400 ml. beaker and make it up to about 200 ml. with water. Add enough hydrochloric acid to lower the pH to between 4 and 5, and filter. Proceed as described under identity tests in the monograph for Sodium Sulfacetamide starting with, "Wash the residue with water . . ."

Assay: (Sulfacetamide) Accurately measure an amount of liquid equivalent to about 0.5 gm. of sodium sulfacetamide. Proceed as described in the assay in the monograph for Sulfadiazine, *U. S. P. XIV,* p. 577, starting with, "Add 20 cc. of hydrochloric acid . . ." The amount of sulfacetamide present is not less than 80.0 nor more than 88.4%, equivalent to not less than 95.0 nor more than 105.0% of the labeled amount of sodium sulfacetamide.

Ophthalmic Ointment Sodium Sulamyd 10%: 3.54 gm. tubes. An ointment containing 0.1 gm. of sodium sulfacetamide in each gm. U. S. Patent 2,411,495. U. S. Trademark 379,386. Schering Corporation, Bloomfield, N. J.

Ophthalmic Solution Sodium Sulamyd 30%: 15 cc. bottles. A solution containing 0.3 gm. of sodium sulfacetamide in each cubic centimeter. Buffered with 0.2% sodium dihydrogen phosphate. Preserved with 0.15% sodium thiosulfate, 0.05% methylparaben and 0.01% propylparaben. U. S. Patent 2,411,495. U. S. Trademark 379,386. Schering Corporation, Bloomfield, N. J.

REPORT OF THE COUNCIL

The Council has authorized publication of the following report from the Committee on Research, a standing Committee of the Council on Pharmacy and Chemistry.

R. T. STORMONT, M.D., *Secretary.*

The Committee on Research has adopted the following status report on "krebiozen" and wishes to express its indebtedness to Dr. Dwight E. Clark, Professor of Surgery, University of Chicago; Dr. Peter A. Nelson, Assistant Clinical Professor of Surgery, Stritch School of Medicine; Dr. P. Shubik, Cancer Coordinator, Chicago Medical School; and Dr. James P. Simonds, Professor Emeritus of Pathology, Northwestern University, who served as a subcommittee in reviewing the accumulated data.

PAUL L. WERMER, M.D., *Secretary.*

A STATUS REPORT ON "KREBIOZEN"

On March 26, 1951, a group of Chicago investigators made a preliminary announcement concerning the effects secured with a drug, "krebiozen," in the treatment of cancer.

In a brochure [1] released simultaneously with the announcement, "krebiozen" was described in vague general terms as a regulator of proliferative activity which controlled the permeability of the body cell or its enzyme systems. It was further postulated that in krebiozen deficient states an increase in anaerobic oxidation and acidity within the cells produces uncontrolled growth and cancer and that when "krebiozen" is supplied, a return to normal growth control occurs. The method of preparation of the drug was shrouded in the following terminology. "Dr. Durovic stimulated the reticulo-endothelial system of the horse and separated from the serum by a chemical process the 'krebiozen' in a pure or almost pure state." The drug was described as a white powder soluble in water, mineral oil, and most organic solvents. It had been supplied to the original investigators by Dr. Stevan Durovic in ampuls containing 0.01 mg. of "krebiozen" in 1 cc. of mineral oil solution. After determining the product's lack of toxicity as evidenced by animal studies it was "standardized" in humans by testing its ability to reduce tumor induration and size in a single case of untreated adenocarcinoma of the breast. Following this "standardization" the material was used in the treatment of 22 patients with cancer. The conclusions drawn can be best summarized by a direct quotation: "On the basis of objective anatomical and clinical evidence, 20 of the 22 cancer patients have shown an improvement in their general condition and a cessation of the growth, and a regression of the cancer which has been consistent and has conformed to a general pattern." Subjective results were reported apparent in one to ten days and objective evidence of tumor regression in 2 to 12 weeks. The presentation was made before a specially invited group of the press, public relations counsel, the laity, and cancer specialists, and excited world-wide comment and interest.

Ordinarily the Committee on Research, as a component part of the Council on Pharmacy and Chemistry, would not attempt to evaluate the clinical benefits, if any, of a substance whose character and method of manufacture were not known and standardization of which was so loosely defined. However, the importunities of physicians for authentic information and the tremendous worldwide public interest created a moral obligation to the profession and to the laity which transcended the issue of medical ethics ordinarily applicable to secret remedies.

The logical first step in such an investigation was to ascertain whether "krebiozen" was actually a secret remedy or whether the investigators had shown justifiable reluctance in disclosing its nature and method of production to the heterogeneous group present at the original announcement. Therefore, a visit was made to the Chicago office of the Krebiozen Research Foundation by the A. M. A. Director of the Bureau of Investigation, an elected American Medical Association official, and the Secretary of the Committee on Research, accompanied by a physician of Yugoslavian ancestry who acted as an interpreter to insure complete understanding during the interview. Dr. Stevan Durovic and his brother, Marko, proved most cooperative in discussing all phases of "krebiozen" investigation and showed the group many letters of testimonial from practitioners. However, when queried as to the exact biologic or chemical nature of "krebiozen," Dr. Durovic referred to the vague original statements made at the announcement. Dr. Durovic refused to amplify his statements in any way, stating that the product might be patented at some future date, that he was afraid that the patent might be violated in some South American country, and that the secret might leak behind the "iron curtain." In subsequent interviews with some of the participants in the study it was disclosed that none of them had ever seen "krebiozen" in any other form but in solution. In the brochure it was reported that "krebiozen" favorably altered tumors occurring spontaneously in cats and dogs. It was disclosed later that these animal studies had been done in Argentina and that the slides alone had been reviewed in this country. All animal studies performed in the United States on tumors occurring spontaneously or induced chemically in mice and rats had shown negative results with "krebiozen."

From the foregoing it is evident that "krebiozen" actually is a secret remedy whose nature and preparation are known only to Dr. Stevan Durovic and, presumably, his brother, Marko.

The next step in the investigation was to secure information on the effects of "krebiozen" which could be suitably analyzed by the Committee on Research. Therefore only clinicians with wide experience in the natural history, course, and therapy of cancer were requested to submit abstracts of their experience with the drug to the Committee on Research. These men had been invited to evaluate the drug by Dr. Ivy and associates in the Krebiozen Research Foundation. Reports were received from seven sources located in four widely separate regions of the country (including the Tumor Clinic, Department of Surgery, University of Illinois). In each instance the directions for use of the drug, as furnished by the original investigators, had been meticulously followed, biopsy specimens prior to treatment had been obtained, and therapy was restricted to "krebiozen" unless the condition of the patients became so grave as to require other control measures of treatment.

CHART 1.—*Distribution of Tumors and Deaths*

	Tumors	Deaths
Gastrointestinal tract	24	11
Breast	22	11 *
Female genital tract	12	3
Lymphatic system	10	8 †
Malignant melanoma	8	3
Respiratory tract	7	3
Skin	6	2 ‡
Urologic	3	0
Skeletal	3	0
Nervous system	2	1
Male genital tract	2	2
Endocrine	2	1
Unclassified sarcoma	2	1
Total tumors	103	46
Total patients	100	44 §

* 1 with another primary growth.
† 2 with another primary growth.
‡ 1 with another primary growth.
§ Corrected total on deaths.

In order to insure that case reports would be evaluated adequately a committee, experienced in the course and long-term care of cancer, composed of faculty members of the medical schools located in Chicago (exclusive of the University of Illinois), served as a review board.

One hundred unselected patients with cancer treated with "krebiozen" have been reviewed (see Chart 1). In three patients two primary neoplastic lesions were found on initial examination. Up to the time of review, 44 deaths had occurred in this series. Two of the deaths occurred in patients with double primaries; therefore, the total deaths in Chart 1 reported as 46 must be corrected to 44.

Apparent objective evidence of improvement was obtained in only two patients; both had been treated in the same institution but by different observers. Ninety-eight patients did not show material alteration in the course or progression of tumor growth, nor significant change in their requirements for narcotic medication, nor significant histopathologic change in involved tissue. In two instances, initial euphoria was reported, and one patient experienced drowsiness following each injection. Summary of all cases reported may be found in the tables accompanying the

1. Ivy, A. C.; Krasno, L.; Phillips, W. F.; Pick, J. F., and Grubgeld, L. E.: Krebiozen: An Agent for the Treatment of Malignant Tumors, Chicago, 1951.

discussion of the cases by systems. The two cases in whom objective improvement seemed to occur are reported in detail.

The first patient (Case 1, Table XI) was a 68-year-old white man who was found to have carcinoma of the prostrate gland in 1945. Bilateral orchiectomy was performed shortly after the diagnosis was established. Between 1945 and 1950, estrogenic hormones had been taken intermittently and in varying doses. The patient remained reasonably well until 1947, at which time onset of urinary frequency was noted. In the latter half of 1950, generalized low back pain developed associated with ascites and dependent edema, at which time a diagnosis of cirrhosis of the liver was also established. A course of deep roentgen ray therapy over the lower lumbar spine and sacrum temporarily relieved pain. However, pain rapidly returned, and on Oct. 16, 1950, he was again incapacitated. Both the acid and alkaline phosphatase levels were moderately elevated. Implantation of progesterone pellets resulted in a temporary remission. The acid phosphatase value became normal, and there was almost complete disappearance of pain. The patient was also placed on a high protein, high vitamin diet for the cirrhosis. Early in January, 1951, phosphatase levels were once again elevated and two doses of 10 mg. of triethylene melamine were administered. The patient became rapidly worse, and by mid-March the acid phosphastase value rose to 11 Bodansky units. The patient was confined to bed and was semicomatose. The blood urea nitrogen

CHART 2

Case Analysis—Gastrointestinal Tract

	Tumors	Deaths
Tongue	3	2
Soft Palate	2	0
Epiglottis	1	1
Esophagus	1	0
Stomach	2	2
Colon	7	3
Rectum	5	1
Pancreas	3	2
	24	11

CHART 3

Case Analysis—Female Genital Tract

	Tumors	Deaths
Uterus	4	..
Cervix	4	1
Ovary	2	2
Vulva	2	..
	12	3

value was elevated to more than 90 mg./per 100 cc., and an intravenous pyelogram indicated one nonfunctioning and one poorly functioning kidney. On April 6 and April 9, 1 cc. of "krebiozen" was given. The patient at this time was disoriented and restless, owing to mild pneumonitis. Gradual recovery occurred with diminution of pain. The blood urea nitrogen level fell to approximately normal levels. There were, however, no demonstrable objective changes in the radiologic appearance of metastases to bone. The patient was strong enough to return home and spent approximately half of his time out of bed. He ate well and gained weight. However, pain in the same areas began to return within a month, and elevation of the acid phosphatase level recurred. Additional treatment with "krebiozen" on May 15, May 18, June 20, June 23, July 18, and July 21 were unavailing. In fact, after the second series of "krebiozen" injections the phosphatase levels rose. On July 10 a single low value for the acid and alkaline phosphatase levels occurred, but this was not accompanied by any improvement in the general condition of the patient. He became progressively worse and died on July 29, 1951.

The observer felt that after each of the last three courses of "krebiozen" the patient experienced increased pain and malaise. In reviewing the case the correspondent further feels that the initial response may have been due to the mild pneumonitis and fever which developed coincident with the first "krebiozen" series. The variability in the acid phosphatase levels following the other injections of "krebiozen" suggests that the initial response was due to coincidence rather than to therapeutic response. This conclusion is further substantiated by a review of the patient's acid and alkaline phosphatase values while under observation, which reveal a constantly fluctuating pattern both on his initial and second admission to the hospital (Chart 9).

The second patient (Case 2, Table XIII) was that of a 40-year-old white man with an admission diagnosis, on March 9, 1951, of sarcoma of the left gluteal region. He gave a history of pain

CHART 4

Case Analysis—Lymphatic System

	Tumors	Deaths
Hodgkins sarcoma	5	3
Lymphatic leukemia	2	2
Acute myelogenous leukemia	1	1
Chronic myelogenous leukemia	1	1
Lymphoblastoma	1	1
	10	8

in the upper left leg and hip of approximately one year's duration. Pain was characterized as recurrent and of gradually increasing severity. In October, 1950, he received osteopathic manipulations of the left hip, after which pain was intensified. In November, 1950, he consulted a physician. Roentgen ray studies showed demineralization of the acetabulum and trochanteric region of the femur and what appeared to be an incomplete fracture line involving the neck of the femur. The patient was advised to avoid weight bearing and to return for reexamination. Pain and disability greatly increased in the ensuing few weeks, and the patient noted the development of a tumor mass in the left gluteal region. On Feb. 8, 1951, he consulted another physician. Roentgen ray studies at this time disclosed destructive bony changes involving the left ilium and the head of the left femur, together with narrowing of the hip joint. A punch biopsy done at this time was reported as unclassified sarcoma of a high grade of malignancy. The patient reported on admission that he had lost approximately 15 pounds (7 kg.) and that he had had a low-grade fever for several weeks. Physical examination of the patient when he was admitted to the hospital yielded positive findings only in the left hip, where an ill-defined, extremely tender tumor mass could be felt between the trochanteric area and the ischial tuberosity. Any motion of the hip elicited extreme pain.

Roentgen ray studies made when the patient was admitted showed a soft tissue tumor of the left upper thigh and gluteal area with secondary extension to the ilium and the ascending ramus of the left ischium, with tumor destruction in the body of the ilium extending to the sacroiliac joint. The chest x-ray at this time was reported as negative, but lytic lesions in the second and tenth left ribs and first right rib were overlooked and found only on subsequent review. A punch biopsy of tissue from the left hip area was performed March 15, 1951; the pathologic diagnosis was unclassified sarcoma. During the patient's first few days in the hospital, several subcutaneous nodules were discovered which underwent extremely rapid growth. On March 28, 1951, a biopsy of one of the subcutaneous nodules on the lower right side of the chest wall was reported as unclassified sarcoma, fibrosarcoma suggested. Many multiple subcutaneous nodules were found in the abdominal wall and several on the right side of the chest, in the xyphoid area. The patient also had

CHART 5

Case Analysis—Respiratory Tract

	Tumors	Deaths
Pulmonary	6	2
Nasopharynx	1	1
	7	3

single lesions in the inner upper aspects of both thighs and a tumor nodule in the right lobe of the thyroid gland. These nodules were extremely sensitive and could barely be touched. On April 1, 1951, a chest x-ray showed, in addition to the lytic lesions of the ribs, a rounded density of the right hilus and a similar rounded density overlying the left hemidiaphragm.

The first course of "krebiozen" consisting of two 10 γ doses intramuscularly was given on April 12 and 15. During the follow-

ing month the subcutaneous nodules, which were observed daily, did not change in size, although no new subcutaneous lesions appeared. The lesion of the right hilus seen on x-ray, however, increased considerably in size. The patient continued on the same dosage of morphine, ate very little, and remained bed-fast. A biopsy of another of the subcutaneous nodules done April 26, 14 days after the first dose of "krebiozen," was reported as showing no difference in the tumor from previous biopsies.

CHART 6

Case Analysis—Skin

	Tumors	Deaths
Squamous cell carcinoma	4	1
Epidermoid carcinoma	2	1
	6	2

CHART 7

Case Analysis—Nervous System

	Tumors	Deaths
Neurogenic sarcoma	1	..
Neuroblastoma	1	1
	2	1

CHART 8

Case Analysis—Male Genital Tract

	Tumors	Deaths
Prostate	1	1
Testes	1	1
	2	2

The first definite changes in clinical course were noted a few days before the second course of "krebiozen" was scheduled to be given. The patient's appetite improved, movement of his left hip became much freer, and it was possible to substitute, for morphine, an acetylsalicylic acid, acetophenetidin, caffeine, and codeine combination containing 65 mg. of codeine and later a similar combination containing 32 mg. of codeine per dose. The second course of "krebiozen" was given May 9 and 12. By May 22, a definite decrease in the size of the nodules of the chest, abdomen, and the thyroid gland was noted.

A third course of "krebiozen" was given May 23 and 26. In the following weeks, continued regression of the tumor nodules was noted. The patient got up and moved about on crutches daily, and a mental state characteristic of euphoria ensued. By July 15, four subcutaneous nodules of the trunk were no longer palpable and the mass over the xyphoid was at least 50% smaller. The nodule of the thyroid gland also could no longer be felt, and the single metastases at the inner aspect of both thighs had decreased by at least 85%. No change occurred in the left gluteal mass. A chest x-ray on July 16 was reported as showing complete disappearance of the right hilar density. No antibiotics were administered during the period of improvement, and the patient was afebrile except for occasional elevations to 99 or 100 F.

A definite relapse became evident about August 15. The patient became depressed and listless and again complained of pain in the left hip, and anorexia developed. Regrowth of the nodule overlying the xyphoid became apparent. Increasing pigmentation of the biopsy scars suggested adrenal insufficiency, and a Thorn test done August 22 did not induce change in the eosinophil counts. "Krebiozen" therapy was resumed August 27, but in mid-September, it had not caused any change in the downward course of the patient, who was then regarded as preterminal.

The skiagrams were reviewed in Chicago by the subcommittee and consultant radiologists, who corroborated the finding that the lesion in the right hilar area observed April 1 disappeared by July 16, but this density was never demonstrated to be tumor. Certainly the osseous lesions showed a steady rapid progression in the films reviewed. The observer suggests that the amelioration noted may have been due to a gradual invasion of the adrenal cortex as later demonstrated by the pigmentation of the biopsy scars and the negative Thorn test.

At best this may be considered a dubious response of metastatic skin and lung lesions but with no alteration of the rapid course and activity of the major osseous lesions.

Among the 98 cases with negative response, there were several patients, noted below, in whom temporary or subjective response might have led less experienced observers to report definite objective improvement. These 98 cases are reviewed briefly by systems.

One patient with abdominal recurrences and liver metastasis following resection for adenocarcinoma of the sigmoid (Case 7, Table I) was given four courses of "krebiozen." Symptomatically, he improved during the first 8 weeks. He gained 3 lbs., required less opiates, and felt strong enough to return to work. Objectively, there was no decrease in abdominal tumor size and the liver metastases definitely increased in size. This man knew he was receiving "krebiozen" and was cognizant of its favorable publicity. Following this initial gain there was a rapid failure, with loss of appetite and weight. At the time of the report he was considered preterminal; his early improvement was regarded as entirely psychogenic and subjective by the investigator.

One patient with carcinoma of the breast (Case 4, Table II) showed a temporary euphoria but rapid objective progression of all lesions and died six weeks after therapy was begun. Another (Case 17, Table II) showed initial exhilaration which subsided in 3 weeks but, objectively, new metastatic lesions appeared despite 5 courses of "krebiozen." In this case, serial biopsy revealed no significant differences in histologic pattern of pre and post treatment tissues. Although ambulant at the beginning of treatment the patient gradually weakened and is now confined to bed. The remaining 20 cases showed no response. One patient (Case 15, Table II) expired within two days of the last injection of the single course and thus lived too short a time for evaluation of drug effect.

None of the 12 cases of female genital tract cancer showed any evidence of objective improvement. One patient with early carcinoma of the cervix (Case 6, Table III) received 4 courses of "krebiozen" and subjectively reported improvement in strength and well being. Objectively, the cervical lesion had progressed to a fungating mass bleeding easily on touch and requiring immediate surgery.

Eight of these patients have expired. One patient with Hodgkins sarcoma (Case 2, Table IV) showed some initial regression in size of tumor masses but this temporary improvement was followed by rapid and sudden progression of all lesions with new lesions developing despite continued "krebiozen" therapy. One patient (Case 7, Table IV) lived too short a time after administration of the drug to permit evaluation.

Three of the eight patients with malignant melanoma expired shortly after "krebiozen" therapy. One patient with widespread metastatic pigmented lesions of the skin (Case 8, Table V), ambulatory at the time of the "krebiozen" course, died within one week of the second injection. The two other patients who died (Cases 3 and 4, Table V) received two courses of "krebiozen" but showed no response and exhibited rapid increase in the size and number of subcutaneous nodules. One of the five patients still living at the time of the report (Case 1, Table V) showed such rapid progression of recurrent tumor involving the right antrum, right nares, and right orbit, that x-ray therapy was

CHART 9

Date	Phosphatase Values Acid	Alkaline	Date	Phosphatase Values Acid	Alkaline
1/ 4/51	3.39	8.37	4/11/51	4.80	7.20
1/11/51	5.90	9.81	4/12/51	3.40	8.44
1/18/51	3.92	12.72	4/13/51	6.40	10.67
1/25/51	2.61	8.90	4/16/51	3.08	6.51
2/ 5/51	4.48	7.17	4/18/51	7.60	15.20
2/13/51	6.96	6.86	4/27/51	4.80	11.86
2/22/51	8.80	4.64	5/ 4/51	7.20	10.30
3/ 2/51	2.64	6.48	5/14/51	9.36	12.50 †
3/13/51	4.20	8.72	5/21/51	11.20	26.30
3/22/51	11.76	5.86	5/28/51	28.80	29.60
4/ 2/51	11.28	3.52	6/13/51	19.20	15.60
4/ 5/51	10.80	5.75	6/19/51	19.20	17.75 ‡
4/ 6/51	9.30	9.28 *	6/28/51	13.00	12.40
4/ 7/51	6.83	6.00	7/10/51	6.72	4.27
4/ 9/51	7.40	8.45 *	7/16/51	21.60	13.10 §
4/10/51	3.32	7.00	7/25/51	22.40	19.25

* "Krebiozen" given.
† "Krebiozen" given 5/15, 5/18.
‡ "Krebiozen" given 6/20, 6/23.
§ "Krebiozen" given 7/18, 7/21.

TABLE I.—*Cancer of Gastrointestinal Tract*

	Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1.	Carcinoma of Tongue	56	F	4 month old untreated carcinoma of tongue involving anterior ⅔ of tongue and floor of mouth	4/ 3/51 4/ 6/51 4/24/51 4/28/51	Steady progression, developed cervical metastases. Expired 5/21/51
2.	Carcinoma of Tongue Carcinoma of Esophagus	62	M	Double primary, epidermoid carcinoma of base of tongue and middle third of esophagus. Irradiated 8/50 and 9/50; thoracotomy, 12/50; esophageal lesion, inoperable. In 5/51 residual disease in both sites and bilateral metastases to cervical nodes	5/19/51 5/22/51 6/23/51 7/17/51	Gradual increase in size of cervical metastases with ultimate coalescence. No other significant changes noted
3.	Carcinoma of Tongue	43	M	No prior treatment, carcinoma involving ⅔ of tongue, cervical node and lung implants	5/22/51 5/25/51	Rapidly progressive disease unaltered by Krebiozen. Expired 5/30/51
4.	Carcinoma of Epiglottis	64	M	Squamous cell carcinoma 10/27/48. Biopsy 11/28/50 transitional cell carcinoma	5/ 4/51 5/ 7/51	No effect noted. Patient continued downward course. Expired 7/51
5.	Carcinoma of Soft Palate	73	F	Developed lesion on soft palate 5/50, excised, irradiated; cervical node metastases by 4/51	4/13/51 4/16/51 5/11/51 5/14/51	No alteration, continued slow involvement of cervical nodes
6.	Carcinoma of Palate	60	M	In 2/51 noticed "sore" in roof of mouth. Diagnosis in 4/51—carcinoma of palate extending into pharynx; no previous treatment	5/11/51 5/14/51 6/ 8/51 6/11/51	No alteration in course of disease; has progressively involved large area. Developed metastasis to right cervical lymph node during therapy
7.	Adenocarcinoma of Sigmoid	54	M	Resection 1948, local recurrence in 11/50, proximal colostomy performed, large mass found filling lower pelvis, fixed to anterior abdominal wall, liver metastases	4/10/51 4/13/51 4/28/51 5/ 1/51 5/29/51 6/30/51 7/28/51	Symptomatically much improved in first 8 weeks, gained 3 lbs., felt stronger, returned to work for 4 hours daily. Objectively no diminution in size of abdominal tumor, liver metastases increased in size. Then appetite failed, lost weight, now preterminal. Improvement psychogenic, no objective improvement on Krebiozen
8.	Adenocarcinoma of Cecum	50	M	Celiotomy 1950, inoperable cancer of cecum, metastases to liver—little pain	4/17/51 4/20/51 5/ 5/51 5/ 8/51 6/ 9/51 6/12/51 7/10/51	Abdominal mass gradually increased in size until fusion of liver and abdominal mass took place. Patient preterminal
9.	Adenocarcinoma of Sigmoid	60	F	Resection in 5/50, recurred 1/51, celiotomy performed 5/51, multiple peritoneal and hepatic metastases	4/24/51 4/27/51	No response. Patient developed intestinal obstruction. Expired 5/1/51
10.	Carcinoma of Ascending Colon	27	F	Right hemicolectomy 10/48. 12/12/50 massive pelvic recurrence and liver metastases; at colostomy, inoperable	4/ 6/51 4/ 9/51 4/24/51 4/28/51 5/19/51 5/21/21	Steady progression of disease, increasing pain throughout observation. Expired 6/2/51
11.	Adenocarcinoma of Splenic Flexure	34	F	Exploratory laparotomy 6/50, inoperable, deep x-ray therapy	2 courses 5/ /51 6/ /51	Had short period of improvement following irradiation. Gradual progression of disease. Patient preterminal
12.	Adenocarcinoma of Colon	51	..	12/49 resection of colon, 11/50 pain in abdomen. Hepatic metastases noted	6/11/51 6/14/51	No change in progress of disease
13.	Cancer of Sigmoid Colon	34	F	Surgical resection. Nitrogen mustard, irradiation	1 course	No alteration in course or progress of disease. Patient died one month after first injection
14.	Cancer of Stomach	52	M	Resection	2 courses	No alteration in course or progress of disease. Patient expired within one month of last injection
15.	Cancer of Stomach	48	M	Diagnosis established at time of celiotomy 12/50, inoperable. At gastroenterostomy performed in 5/51, patient had large fixed mass in abdomen, multiple metastases to liver	5/ 9/51 5/12/51	Abdominal tumor masses increased rapidly in size. Weakness and anorexia became severe. Ascites developed, patient expired 6/6/51
16.	Cancer of Rectum	66	F	Surgery	2 courses	Died with no apparent results either subjective or objective to treatment
17.	Cancer of Rectum	..	F	Fungating growth in rectum, bleeds easily	3 courses	Progressive course, bleeding friable tumor
18.	Cancer of Rectum	..	M	Polypoid lesion of rectum	2 courses 4/ /51 5/ /51	Gradual progression in growth of tumor mass
19.	Adenocarcinoma of Rectum	48	F	Infiltrating adenocarcinoma of rectum, 9/29/48, slowly progressing	5/15/51 5/18/51 7/19/51 7/23/51	Continued slow progression. No subjective or objective improvement. No evidence of alteration. Now involving pelvis and sacrum
20.	Adenocarcinoma of Rectum	32	F	Adenocarcinoma extending thru muscularis into fat and fibrous connective tissue	1 course	No response. Continued progression
21.	Adenocarcinoma of Pancreas	54	M	Cholecystojejunostomy and jejunojejunostomy	5/ 1/51 5/18/51 6/14/51 7/14/51	No change in slow progression of disease, requires same amount of opiates
22.	Liposarcoma of Pancreas	47	M	None—exploratory laparotomy 3/23/51	4/11/51 4/14/51	No response. No change in size of abdominal tumor or clinical course. Expired 4/29/51. Probably myocardial infarction
23.	Adenocarcinoma of Pancreas	61	M	In 1/51 developed supraclavicular node, by 4/51 large fixed abdominal mass attached to anterior abdominal wall	4/10/51 4/13/51 4/27/51 4/29/51	No regression of any demonstrable tumor. Growth of metastases in neck caused acute respiratory obstruction. Expired 5/3/51. Biopsy prior to death and autopsy specimen showed no effect on histologic character of tumor

begun. The remaining four patients showed no subjective evidence of improvement and, objectively, the lesions were progressing. Similarly, the seven patients with respiratory tract cancer showed no objective or subjective evidence of improvement. One patient with bronchogenic carcinoma of the lung (Case 3, Table VI) expired after two courses of therapy and another (Case 4, Table VI) died within a month after a single course.

The patients with cancer of the skin exhibited no response to "krebiozen" therapy. All cases showed progression of lesions objectively. One patient (Case 4, Table VIII) with concomitant

TABLE II.—*Carcinoma of Breast*

	Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1.	Carcinoma of Breast	47	F	Hormones	2 courses	Progressing in severity, no influence on course or progress
2.	Carcinoma of Breast	57	F	Surgery, widespread metastases	1 course	No alteration in clinical or pathologic course. Expired (date not given)
3.	Carcinoma of Breast	70	F	Surgery, irradiation, hormones; slowly progressive	1 course	Continued to progress slowly downhill, new metastatic lesions, no observable change in course due to therapy
4.	Carcinoma of Breast	42	F	Surgery, irradiation, hormones; rapidly progressive metastases	1 course	Temporary euphoria, rapidly progressing objectively, died 6 weeks after Krebiozen; no observable change in course
5.	Adenocarcinoma of Breast Grade 3	81	F	One-year history of lesion in left breast; ulceration several months. No prior treatment. Slowly progressing	5/ 8/51 5/11/51 6/12/51 6/15/51	Drowsy after each injection, no measurable change in size of mass, ulcer or nodes thru 7/31/51; continued slow progression
6.	Carcinoma Simplex of Breast	50	F	Radical mastectomy 1944; 1947 recurrence; hormones, irradiation, castration; disease quiescent 5/49. Then steady progression of skin involvement over thoracic cage with confluent nodules right pleura solid with tumor. Last x-ray therapy 2/51	5/ 8/51 5/11/51 6/12/51 6/15/51	Continued slow progression of disease over left post thorax, left breast, right supraclavicular area, anemia persists—no effect
7.	Carcinoma of Left Breast	61	F	No prior treatment; metastases to liver, rapidly progressing	4/ 5/51 4/ 8/51	One course; no change in rapid downhill course. Expired 5/3/51
8.	Carcinoma Simplex of Left Breast	52	F	Disease diagnosed 6/30/49; metastases to lymph nodes, progressing despite hormone therapy	4/ 3/51 4/ 6/51 5/ 9/51 5/14/51	No change in progressive downhill course, no alteration in size or number of lesions, new metastases. Expired 8/11/51
9.	Carcinoma Simplex of Left Breast	27	F	Biopsy 3/26/51—axillary metastases rapidly progressing	6/ 1/51 6/ 4/51	Extremely rapid course unaltered by Krebiozen. Expired 8/19/51
10.	Carcinoma of Left Breast	42	F	Inoperable Carcinoma of left breast. Multiple metastases—progressing slowly	2 courses	No subjective or objective improvement, no evidence of change in size of tumor or alteration of course of disease
11.	Infiltrating Adenocarcinoma	46	F	Biopsy 1/2/51 rapidly progressing inoperable Carcinoma of breast, multiple metastases	5/ 7/51 5/10/51	No alteration of rapid progression, no subjective or objective improvement. Expired 5/24/51
12.	Carcinoma of Right Breast	52	F	Radical mastectomy 7/49 and irradiation. At admission cerebral metastases	4/20/51 4/23/51	No response, continuation of typical clinical course of increasing intracranial pressure. Expired 5/3/51. No change in tumor cells or growth pattern on pathologic examination
13.	Carcinoma of Left Breast	54	F	Biopsy 10/13/50, carcinoma a simplex left breast, early	5 courses	Very active cancer growth has occurred since 4/51, lump in biopsy scar enlarging, orange peel skin
14.	Adenocarcinoma of Breast	41	F	Biopsy 2/50, early carcinoma	4 courses	Patient has extension of disease, pain in both axillae, lymph node palpable in right supraclavicular area, slow progression
15.	Adenocarcinoma of Breast	51	F	Radical mastectomy 1949, x-ray therapy, 3 courses, last in 5/51, castrated	1 course	Expired within 2 days of last injection, impossible to evaluate
16.	Adenocarcinoma of Breast	62	F	Primary adenocarcinoma of breast. Advanced carcinoma diagnosed 3/47, inoperable, irradiated, slowly progressing, involves anterior chest wall	4/26/51 4/29/51 5/28/51 5/31/51	No alteration in course—slowly progressing
17.	Adenocarcinoma of Right Breast	55	F	Diagnosed in 1938—radical mastectomy—local recurrence in 1943, excised and irradiated, hormonal therapy, slowly progressing, ambulant	4/ 3/51 4/ 6/51 4/21/51 4/24/51 5/12/51 6/11/51 6/19/51 7/10/51 7/24/51	Initial exhilaration subsided in 3 weeks, objectively new lesions appeared, old lesions relatively stationary, biopsy shows no significant differences in histologic pattern of pre and post treatment tissue, no longer ambulant, sinking
18.	Adenocarcinoma of Left Breast	61	F	Radical mastectomy 5/48, recurrent in one year, to opposite breast, lung and bone; irradiated, hormones, poor response	4/10/51 4/13/51 4/27/51 4/29/51 5/14/51	All lesions increased in size both in irradiated and non-irradiated areas, pleural effusion appeared—expired 6/11/51. Necropsy—no microscopic evidence of alteration in histologic pattern
19.	Carcinoma of Breast	61	F	Lump noted since 4/50—no treatment. By 4/6/51 large ulcerating mass in right breast, fixed axillary metastases	4/10/51 4/13/51 4/28/51 5/ 1/51	Tumor mass increasing slowly in size, pain more severe. Required large doses of narcotics. Condition so poor removed from Krebiozen, placed on estrogen. Biopsy, pretreatment, and 18 days after last injection; comparison of two specimens reveals no differences in cellular detail or configuration that are not attributable to different locations or tissue sites
20.	Carcinoma of Left Breast	..	F	Mastectomy 1949—recurrence in 1951. Multiple osseous and axillary metastases. Postoperative irradiation and two subsequent courses, hormones till 3/51	4/12/51 4/15/51 5/ 2/51 5/ 5/51 5/26/51	No change in calcium balance, many new skin nodules developed over scalp, new osteolytic lesions, pain increased
21.	Carcinoma of Right Breast	57	F	Mastectomy 6/49. Multiple metastases within 1 year involving spine, pelvis, liver, and chest wall	5/ 7/51 5/ 9/51 5/26/51 5/29/51	No change in progress of disease, osseous lesions revealed no change on x-ray examination, marked increase in pain, required 3 times amount of opiates. Expired 7/14/51
22.	Carcinoma of Breast; Chronic Myelogenous leukemia (Double primary—see case 10, Table IV)	50	F	Prior treatment unavailable	5/12/51 5/15/51 5/29/51	Patient was given concurrent irradiation to breast by private practitioner. Despite treatment showed progression of mammary tumor, bone marrow studies failed to reveal any influence on leukemia. Modified radical mastectomy performed elsewhere 6/10/51. Patient expired 6/18/51, acute leukemic exacerbation

Hodgkins sarcoma expired despite two courses of therapy. Another patient with epidermoid carcinoma arising in the left axilla (Case 6, Table VIII) showed rapid expansion of all metastatic lesions and dried after three courses of "krebiozen." No response was elicited with "krebiozen" therapy; repeated cystoscopic examination showed further growth of the lesions in

TABLE III.—*Cancer of Female Genital Tract*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Carcinoma of Uterus	56	F	Adenocarcinoma of uterus with considerable bleeding, frozen pelvis	5 courses	Has continued to show progression of disease with continued bleeding. Slow downhill course
2. Carcinoma of Uterus	47	F	Endometrial carcinoma with extension into bowel, considerable bleeding	2 courses	No improvement noted, bleeding becoming more severe, to have x-ray therapy
3. Carcinoma of Uterus	46	F	Complete hysterectomy 1947 followed by irradiation therapy. Nodes noted 11/50 inguinal region	6 courses	Actively progressing disease despite treatment, now inoperable
4. Carcinoma of Uterus	..	F	No information received	1 course	No response noted. Disease progressing
5. Carcinoma of Cervix	39	F	Subtotal hysterectomy 9/49. Adenocarcinoma of cervix reported in stump 7/50. Radon treatment, gradual extension through pelvis, ambulant	3 courses	Pain in back more severe, patient weaker. Now requires hospitalization. No alteration of progress of disease
6. Carcinoma of Cervix	39	F	Following hemorrhage in 3/51, diagnostic curettage revealed adenocarcinoma of cervix. No therapy	4 courses	Subjectively patient feels better, but objectively the cervical lesion has progressed. Now is a fungating mass bleeding easily on touch. To have surgery
7. Carcinoma of Cervix	56	F	No information received	6/12/51 6/15/51	No subjective or objective improvement, lesion progressing. To have surgery
8. Carcinoma of Cervix	46	F	Transitional cell carcinoma of cervix 1/4/51. 5/1/51 diagnosed as epidermoid carcinoma	4/13/51 4/16/51 5/ 2/51	No alteration in course of disease. Rapidly progressive disease involving entire pelvis and adnexae. Expired 6/25/51
9. Carcinoma of Ovary	65	F	Adenocarcinoma of ovary diagnosed on surgical exploration in 1949, irradiation following. Disease was advanced with metastases to abdominal organs and wall	3 injections	No alteration in course and progression of disease. Expired 6/5/51
10. Carcinoma of Ovary	61	F	Adenocarcinoma of ovary with multiple metastases to abdominal wall and organs	2 courses	No noticeable effect noted. Patient continued sharp downhill course. Expired (date not reported)
11. Squamous Cell Carcinoma of Vulva	44	F	Biopsy 9/50 of lesion: squamous cell carcinoma of vulva, treated with x-ray	3 courses	Slowly progressing lesion. No apparent effect on course of lesion
12. Carcinoma of Vulva	85	F	Diagnosed in 1948. 2 courses of irradiation; 5/51 has ulcerating lesion involving entire vulvar area with metastases to both inguinal areas	2 courses	Active growth continues. Further extension and involvement.

TABLE IV.—*Lymphatic System*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Hodgkins Sarcoma	22	M	Radical neck dissection, 5/50, recurrence 11/50. Nitrogen mustard and x-ray therapy to 2/51. Pulmonary and retroperitoneal involvement and multiple cervical nodes, right	4/24/51 4/27/51 5/15/51 5/18/51	Progressive unaltered course, failed to respond to ACTH administered 5/16/51; expired 5/23/51
2. Hodgkins Sarcoma	27	M	Diagnosed 7/47. Gradual spread to generalized lymphadenopathy and intrapulmonary disease. Multiple courses of radiation ending 12/50. Nitrogen mustard 3/27 to 4/3/50. In 1/51 triethylene melamine orally. Apparently x-ray and nitrogen mustard-fast	4/28/51 5/ 1/51 5/26/51 5/29/51 6/30/51	Initially some regression in size; felt better, then sudden progression of all lesions with new lesions developing. Krebiozen discontinued, placed on x-ray therapy
3. Hodgkins Sarcoma	18	F	1/50 diagnosed, course of x-ray therapy 5/50. By 5/51 multiple subcutaneous nodules over back and chest, extensive cervical and mediastinal nodes with significant pulmonary involvement and right pleural effusion	5/ 5/51 5/ 8/51	Dyspnea and tachycardia so severe by 5/28/51 placed on triethylene melamine. Krebiozen regarded failure
4. Hodgkins Sarcoma; Squamous Cell Carcinoma Right Cheek (see Case 4, Table VII)	67	M	No previous treatment, bilateral cervical nodes; mediastinal involvement	4/23/51 4/26/51 5/30/51 6/ 2/51	No response, rapidly progressive growth produced obstructive dyspnea 6/12/51. Placed on x-ray therapy. Died 6/27/51, massive upper gastrointestinal bleeding. Necropsy — large benign gastric ulcer with open sclerotic artery in base. Mediastinal, periaortic, and peripancreatic nodes of typical nature at necropsy—no "Krebiozen effect"
5. Hodgkins Sarcoma	26	M	Bilateral cervical nodes, mediastinal involvement	3 courses	No response, rapidly progressive growth, obstructive dyspnea; expired two weeks after last injection
6. Acute Lymphatic Leukemia	42	M	Irradiation, nitrogen mustard, cortisone, aminopterin, triethylene melamine	1 course	Expired shortly after completion of first course, no apparent alteration in course or progress of disease
7. Acute Myelogenous Leukemia	45	M	Methopterin 2½ mg. 5/11, 5/16. Crystalline penicillin daily, 5 transfusions	5/23/51	Expired 5/24/51—too short a time to evaluate drug
8. Lymphatic Leukemia	42	M	First seen 4/51	1 course	Progressive course, despite transfusions, expired 5/5/51
9. Lymphoblastoma	62	M	Diagnosed in '45. Several courses of irradiation. In 4/51 generalized adenopathy enlarged liver and spleen; bone marrow hypoplastic	4/21/51 4/24/51 5/ 5/51 5/ 8/51 5/29/51	Progressive course, increased anemia, weakness, unable to return to hospital for further treatment. Expired 7/11/51
10. Chronic Myelogenous Leukemia and Carcinoma of breast. (Double primary. See Case 22, Table II)	50	F	.....	5/12/51 5/15/51 5/29/51	Expired 6/18/51

two patients with bladder tumors. All three patients with skeletal system tumor showed unaltered progression of their disease. One patient with endothelial myeloma (Case 3, Table IX) responded promptly, though temporarily, to roentgen ray irradiation given between courses of apparently ineffectual "krebiozen" therapy.

Rapid progression of tumor growth was noted in both cases. In the serial biopsies obtained from the patient with neurogenic sarcoma (Case 1, Table X) the microscopic sections revealed increasing anaplasia under treatment (4½ courses).

The patient with carcinoma of the prostate has been previously described as showing an equivocal response. The other patient with an embryonal carcinoma of the testes expired shortly after the last injection of the initial course.

DISCUSSION

Ivy and his associates have reported beneficial effects in a large majority of patients with cancer treated with "krebiozen." The experience of the seven investigators cited in this report does not agree with this conclusion. Not one of the patients observed has shown any appreciable alteration in the course of the primary tumor growth, although two patients showed equivocal, temporary response. One of these patients had shown a similar pattern

TABLE V.—*Malignant Melanoma*

	Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Courses
1.	Malignant Melanoma Right Orbit	57	F	Malignant melanoma right orbit, removed 1/50. Radium therapy: extensive recurrent tumor 5/51 in right antrum and orbit with exophthalmus and protruding bleeding mass from right nares	5/26/51 5/29/51	Lesion progressed so rapidly in size with increased bleeding and exophthalmus that Krebiozen discontinued. X-ray therapy started
2.	Malignant Melanoma right eye	36	M	Right eye enucleated 1946, in 6/51 multiple metastases, skin nodules	6/15/51 6/18/51	Observed for 2 weeks—no change of progression or evidence of Krebiozen effect observed
3.	Malignant Melanoma primary, unknown	56	F	Diagnosed 11/50. Roentgen therapy 12/50, metastasis to lymph nodes. Skin, lungs, pleura, liver, ribs, pelvis, adrenals and brain	4/ 2/51 4/ 5/51 5/ 1/51 5/ 4/51	No response, increase in size of subcutaneous nodules, appearance and growth of many new nodules. Expired 6/4/51. Necropsy—saturation metastasis—tumor necrosis showing anatomic distribution, i. e., usual tumor necrosis, no Krebiozen effect
4.	Malignant Melanoma primary, unknown	38	M	Pituitary irradiation elsewhere, 1/51. Stilbestrol elsewhere during Jan., Feb. In 3/51 left axillary node, multiple metastases skin, brain, adrenals, and heart	4/ 2/51 4/ 5/51 5/ 1/51 5/ 4/51	No response, increase in size of subcutaneous nodules. Steady deterioration. Expired 6/11/51. Necropsy. Amount and character of tumor necrosis in no way unusual
5.	Malignant Melanoma	12	M	Roentgen therapy 7500 R to supraclavicular node 3/10/51	5/ 7/51 5/12/51 6/ 9/51 6/12/51	No response, increase in size of irradiated nodule and appearance of another on opposite side 7/51
6.	Malignant Melanoma	30	F	Multiple metastasic lesions after surgery	2 courses	No alteration in the clinical or laboratory course. Cancerous lesions rapidly expanding
7.	Malignant Melanoma	45	F	Melano-carcinoma. Surgery for primary with recurrences	1 course	No alteration in progression of disease
8.	Malignant Melanoma	42	M	Excision of lesion of back, 3/51. Multiple lymph gland involvement 4/51. Given course of x-ray elsewhere. Ambulatory—widespread pigmented lesions of skin	5/ 7/51 5/10/51	Although ambulatory 5/7/51 patient had rapid progressive course. Expired 5/17/51

TABLE VI.—*Respiratory Tract*

	Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1.	Carcinoma of Lung	55	M	Advanced local disease with pleural implants. Thoracotomy 1/22/51, inoperable. No treatment. Bronchogenic carcinoma	4/ 3/51 4/ 6/51 4/21/51 4/24/51 5/12/51	Symptomatically became more dyspneic, developed clubbing and cyanosis of fingers. X-ray examination revealed rapid extensive progression of lesions in pulmonary field. X-ray therapy relieved dyspnea. Hospitalized 7/10/51 as preterminal
2.	Carcinoma of Lung	59	F	Diagnosis established 11/50. Primary bronchogenic with supraclavicular and mediastinal metastases. Inoperable, radon implants to mediastinum 11/50; in 4/51—cough dyspnea, hoarseness, anorexia	4/18/51 4/21/51 5/ 5/51 5/ 8/51 5/28/51 6/21/51	Dyspnea became more marked necessitating thoracentesis 5/19/51 and nitrogen mustard 5/20 then 5/29, with temporary relief of dyspnea; lesions showed progression. Now preterminal
3.	Carcinoma of Lung	60	M	Inoperable bronchogenic carcinoma with pleural implants 3/17/51	4/10/51 4/13/51 4/28/51 5/ 1/51	Rapid progression of disease, hemoptysis, pleural effusion and increased pain and anorexia. Pain uncontrolled. Expired 6/29/51
4.	Carcinoma of Lung	64	M	Following surgery developed pleural and mediastinal implants	1 course	Rapid progression of disease. Expired within 1 month of last injection
5.	Carcinoma of Lung	62	M	Inoperable bronchogenic carcinoma with supraclavicular and mediastinal implants. Irradiation and nitrogen mustard treatment	1 course	No change in course of disease, dyspnea became more marked. X-ray reveals progression. To have nitrogen mustard. No subjective or objective improvement
6.	Carcinoma of Lung	..	M	Adenocarcinoma of right lung	6/18/51 6/21/51	No change in the course of disease. Patient sinking rapidly
7.	Carcinoma of nasopharynx	38	M	Epidermoid carcinoma of left nares. 11/45 treated with radon. 4/51 cervical metastases and bilateral pleural effusion, right hypoglossal and glossopharyngeal nerves paralyzed	5/ 1/51 5/ 4/51	Rapidly progressive disease unaltered by therapy. Pulmonary metastases showed rapid extensive progression. Expired 6/15/51. Necropsy—no Krebiozen effect discernible

The adrenal cortical tumor possibly receded in size in the first week after therapy but the patient expired before the second course was due. Despite three courses of therapy the first patient's thyroid tumor progressed and his lung metastases increased in size and number as shown by serial radiographic studies.

Two cases of unclassified sarcoma were reported. One patient has been previously reviewed as showing an equivocal response to therapy. The other patient showed no retardation of tumor growth, rapidly became weaker, and expired five weeks after the third injection of "krebiozen."

of remission and exacerbation prior to the treatment, and later therapy with "krebiozen" failed to show favorable influence. The second patient showed regression of subcutaneous nodules, disappearance of a right hilar density, and great subjective improvement, but his osseous tumors continued to show rapid progression. This may be considered a dubious response of cutaneous and possible pulmonary metastases. This patient has also failed to respond to further courses of "krebiozen" therapy and was considered preterminal.

TABLE VII.—*Skin*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Squamous cell carcinoma Grade III	58	M	First diagnosed 8/49, excision skin interscapular area. 6/50 lymph node involvement; 9/50 and 11/50 excision of basal cell carcinoma of neck and nose. 2/51 recurrent disease of back with lymph node involvement in right and left supraclavicular area and left axilla	5/14/51 5/17/51 6/15/51 6/18/51	At time of last injection new nodules on posterior part of neck. 2 weeks later new nodules around periphery of lesion on neck. Progression unaffected by Krebiozen
2. Squamous cell carcinoma of right cheek and ear	67	M	Deeply ulcerated lesion 10 x 14 cm. Radium 10/50, irradiated 1/51 and 2/51	6/25/51 6/28/51 7/16/51 7/19/51	No response. Definite increase in size of tumor. Pain and trismus worse
3. Squamous cell carcinoma of left ear	72	M	One year history of rapidly developing squamous cell carcinoma of left ear with massive cervical node metastases. No previous treatment	6/ 4/51 6/ 7/51	No response or change noted in 1 week observation
4. Squamous cell carcinoma of right cheek. Hodgkins disease (Double primary; see Case 4, Table IV)	67	M	No previous treatment. 6 mo. history of Hodgkins sarcoma of right cervical and mediastinal nodes. Squamous cell carcinoma of right cheek	4/23/51 4/26/51 5/30/51 6/ 2/51	No response. Rapid enlargement of cervical nodes. Definite increase in size of squamous lesion of right chest. Expired 6/27/51. Autopsy typical Hodgkins. No "Krebiozen effect"
5. Epidermoid carcinoma of left cheek	60	F	First diagnosed in 1924, multiple course of x-ray therapy, last in 1/51. Now extensive ulcerating recurrence, multiple left cervical metastases. Maxillary invasion	5/19/51 5/21/51 6/16/51 6/30/51	Recurrent tumor and metastatic lesions continued to increase in size, new metastases appeared, pain became significant. Biopsy prior to treatment and 28 days after first injection. "Both specimens showed actively growing epidermoid carcinoma of similar histologic quality"
6. Epidermoid carcinoma of left axilla	66	F	8/50—nodule in axilla. Axillary dissection 12/50. X-ray therapy with minimal regression	4/ 3/51 4/ 6/51 4/21/51 4/24/51 5/ 8/51 5/11/51	Tumor masses rapidly increased in size and number, pain increased and poorly controlled. Expired 6/26/51

TABLE VIII.—*Urinary System*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Carcinoma of Kidney	42	F	Diagnosis established 11/50, exploratory laparotomy and liver biopsy. Roentgen therapy to osseous metastases in lumbar spine	4/16/51 4/19/51 5/10/51 5/13/51 6/ 5/51 6/ 8/51	No response, abdominal mass approximately same size, but bone destruction increased on serial films. Increased pain and analgesic requirement. Bilateral chordotomy required 6/51
2. Carcinoma of bladder	66	M	Transitional cell carcinoma of bladder first diagnosed 1934. Repeatedly fulgurated. In 5/51 multiple recurrent areas noted on cystoscopic examinations	5/ 7/51 5/10/51	No "Krebiozen effect" repeated cystoscopic examination during 21 days of observation showed progress, therefore fulguration repeated
3. Carcinoma of bladder	75	M	Cystoscopy and biopsy revealed epidermoid carcinoma of bladder	5/ 7/51 5/10/51	No change in tumor growth observed during repeated cystoscopic examination, therefore tumor removed surgically 5/24/51. No alteration in histologic pattern of biopsy specimens taken 12 and 17 days after Krebiozen

TABLE IX.—*Skeletal System*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Fibrosarcoma of right thigh	22	F	Surgical removal of tumor 8/49, 11/50 pulmonary metastases right upper lobe; thoracotomy and lobectomy. 12/50 local recurrence disarticulation of right hip. 4/51 recurrence in apex right lung field, metastatic nodule in left lower lobe	4/18/51 4/21/51 5/ 5/51 5/ 8/51 6/ 9/51 6/12/51	All pulmonary lesions increased in size while under therapy in manner consistent with natural course of disease, multiple new nodules developed—placed on nitrogen mustard
2. Fibrosarcoma of right thigh	31	F	Diagnosed 12/50, amputation advised but refused, irradiation Feb.-Mar. 1951	4/11/51 4/14/51 5/ 5/51 5/ 8/51 5/22/51	Active progression of disease despite x-ray treatment and Krebiozen
3. Endothelial myeloma (Ewings Tumor)	8	F	Diagnosed 1/50—right humerus lesion resected with fibular graft 8/23/50 following irradiation therapy. Recurrence 3/17/51 at primary site and pulmonary metastases evident	4/ 3/51 4/ 6/51 4/21/51 4/24/51 5/12/51 5/15/51 6/ 9/51 6/12/51	Full 1 cc. injection given. Tumor of right arm progressively enlarged causing impending skin ulceration. Pulmonary metastases increasing in size on serial chest films, metastasis developed in left upper maxilla and retro-orbital area. X-radiation to arm, jaw and eye caused prompt regression during 5/51 but new metastases developed in lumbar vertebra and abdomen in 6/51

TABLE X.—*Nervous System*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Neurogenic sarcoma	15	M	Surgical removal of neurogenic sarcoma of upper lip 1947. Numerous recurrences treated by surgical excision and irradiation. 4/51 recurrence at root of nose near left inner canthus	4/ 6/51 4/10/51 5/ 5/51 5/ 8/51 6/ 9/51 6/12/51 7/10/51	Nodule increased fairly rapidly in size during initial 3½ weeks, partially removed surgically at this time. Continued growth occurred under therapy. Required surgery again 7/14/51. Microscopic sections revealed increasing anaplasia in later sections
2. Neuroblastoma	4	M	No previous treatment	5/ 3/51 5/ 6/51 6/ 1/51 6/ 4/51	No improvement noted. Continued downhill course. Died July 9, 1951

In the brochure, the agent is stated to cause a central necrosis of the tumor and vacuolization and degeneration of cancer cells followed by leukocyte infiltration. The biopsy and necropsy specimens obtained in this series are reported to have failed to show histologic changes attributed to "krebiozen" or in any way inconsistent with the usual course of the pathologic process.

The public may wonder at the wide divergence of opinion between the original report and these published results. Possibly a review of the pitfalls to be avoided in the clinical investigation of a cancer remedy may disclose how these discrepancies might occur. The subjective response of the patient is probably the most misleading and undependable single observation in cancer investigation. To those familiar with the long term care of cancer patients the unreliability of subjective response is notorious. Pain relief, appetite, ambulation, and speech are all affected by the subjective response of the patient to therapy, and therefore, should not be relied upon as evidence of therapeutic efficacy. As an illustration of the dissociation of the feeling tone of the patient from the actual progress of tumor growth, a recent study [2] of the effects of cortisone and corticotropin upon patients in late stages of mammary carcinoma reported that patients had a remarkable feeling of well-being and strength accompanied by relative freedom from pain and increased appetite and ambulation which persisted to practically the day of death. Objectively, these same patients showed acceleration and dissemination of tumor growth.

The investigator too must know the natural course of untreated cancer in order not to be misled by fluctuations in the condition of the patient explainable by that natural course. Finally, it is imperative for the investigator to secure absolute objective evidence of therapeutic effect upon cancer growth by mensuration, biopsy, x-ray technics, photographs and various laboratory procedures. Regression of isolated metastatic lesions while other lesions are progressing should not be considered a therapeutic response. It is imperative that all the lesions in the patient be considered. These principles have been ably restated and summarized in a recent communication.[3]

To the layman, the diagnosis of cancer means an invariably rapid and lethal illness. Thus, to the public, the often extended course of certain types of cancer and the sharp fluctuations in the general condition of the patient come as an unexpected surprise and may serve to lend authenticity to the supposed efficacy of a remedy. The profession generally is aware of this variation in cancer type and therapeutic response, but the public must be dissuaded from the belief that all forms of cancer represent a single disease which progresses in the same manner, by the same course, and responds uniformly to therapy. No therapeutic agent yet investigated materially alters the course of more than a few types of cancer. However desirable, it is most unlikely that a new therapeutic agent would favorably affect all types of cancer.

TABLE XI.—*Male Genital Tract*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Carcinoma of Prostate	68	M	Carcinoma of prostate, metastases to dorsolumbar spine and pelvis. Transurethral resection & orchidectomy 6/45. Irradiation, hormone therapy, 2/51 and 3/51	4/ 6/51 4/ 9/51 5/15/51 5/18/51 6/20/51 6/23/51 7/18/51 7/21/51	Definite decrease in bone pain, fall in acid phosphatase. 10.8 BU 4/5/51 to 3.08 BU 4/16/51. Probably ascribable to cessation of hormone therapy & mild fever from pneumonitis. Sharp relapse within 1 month with no further response to Krebiozen. Expired 7/29/51
2. Carcinoma of Testes	36	M	Embryonal carcinoma 1/50 on biopsy. Multiple metastases to skeletal system.	4/27/51 4/30/51	Rapid downhill course unaltered by Krebiozen therapy. Expired 5/3/51

TABLE XII—*Endocrine System*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Carcinoma of Thyroid	55	M	Papillary carcinoma of thyroid with lung metastases. Slowly progressing. Surgery in 1946, irradiation and surgery 1948, lung metastases 1950	5/ 4/51 5/ 7/51 6/ 5/51 6/11/51 7/12/51 7/17/51	Gradual increase in size and number of metastases during therapy. Lung involvement increasing as noted by serial plates
2. Carcinoma of Adrenal cortex	55	M	Inoperable tumor of adrenal cortex	4/28/51 5/ 1/51	Impression that tumor receded in size during first week, no other change, narcotic requirements same, expired 5/27/51

TABLE XIII.—*Unclassified Sarcoma*

Diagnosis	Age	Sex	Prior Treatment and Course	Krebiozen	Results and Course
1. Unclassified sarcoma	42	M	Diagnosed at laparotomy 4/51. Inoperable, 3 large discrete abdominal masses differentiation as to specific type not possible	5/ 5/51 5/ 8/51 5/29/51	No retardation of tumor growth noted, abdominal masses increased in size and coalesced filled abdomen. Expired 7/5/51
2. Unclassified sarcoma	40	M	Impossible to differentiate sarcoma arising in left gluteal region involving left femoral head ilium, metastases thyroid and right lung	4/12/51 4/15/51 5/ 9/51 5/12/51 5/23/51 5/26/51 6/20/51 6/23/51 7/18/51 7/21/51 8/27/51 8/30/51 9/14/51 9/17/51	Gradual disappearance of 4 biopsied subcutaneous metastases and 50% regression of others, clearing of right hilar density, calcification of pathologic fractures of ribs and left femoral head. Fifteen pounds weight gain. Analgesic requirement lessened. 8/15, returned to hospital with recurrence, weight loss, no response to Krebiozen two courses, considered preterminal

CONCLUSIONS

1. Case histories of 100 patients with cancer treated with a secret remedy, "krebiozen," were obtained from seven independent sources. These histories were carefully reviewed by a subcommittee of the Committee on Research.

2. Ninety-eight patients were reported as failing to show objective evidence of improvement.

3. Two patients showed some evidence of temporary improvement coincident with "krebiozen" therapy. In one patient, this was apparently fortuitous; in the other, the major lesions showed continued rapid progression.

4. Forty-four of the one hundred patients treated have expired.

2. Taylor, S.: Report to Subcommittee on Steroids and Cancer, to be published.

3. Rhoads, C. P.: Science **114**: 285 (Sept. 14) 1951.

5. In the group of patients from whom serial biopsy or autopsy specimens were obtained "krebiozen" failed to show any discernible histologic effect upon tumor.

6. These findings fail to confirm the beneficial effects reported by Ivy and associates.

ADDENDUM

On Oct. 18, 1951, Dr. Ivy accompanied by Dr. Pick appeared before the subcommittee and staff members of the Division of Therapy and Research of the American Medical Association. He voluntarily divulged confidential information given to him by Dr. Durovic concerning the identity of the material injected into the horse to stimulate its reticuloendothelial system. The theoretical basis for use of the substance was discussed. No evidence was presented that stimulation of the reticuloendothelial system actually occurred. The method of extraction and purification of "krebiozen" was not disclosed since such information was stated to be a business secret. Dr. Ivy could give no additional data concerning the chemical and physical nature of the agent and reaffirmed that neither he nor his associates had ever seen "krebiozen" in the pure state. On the basis of the material divulged, it was the opinion of the subcommittee and the others present that "krebiozen" still constituted a secret remedy since adequate data concerning its physical and chemical properties were not presented.

COUNCIL ON PHYSICAL MEDICINE AND REHABILITATION

The Council on Physical Medicine and Rehabilitation has authorized publication of the following reports.

RALPH E. DE FOREST, M.D., *Secretary.*

BIRTCHER ELECTROSURGICAL UNIT 799-H ACCEPTED

Manufacturer: The Birtcher Corporation, 5087 Huntington Drive, Los Angeles 32.

The Birtcher Electrosurgical Unit 799-H is a generator of both undamped (tube-generated) and damped (spark gap) currents designed for use in all the techniques of electrosurgery. The tube-generated current, recommended for cutting, and the spark gap current, recommended for coagulation, can be controlled independently and used simultaneously.

Birtcher Electrosurgical Unit 799-H

The apparatus stands on the floor, is provided with casters, and measures 95 (height) by 67 by 50 cm. (38 by 25 by 19½ in.). It weighs 59 kg. (130 lb.). Prepared for shipment it measures 125 by 76 by 55 cm. (49 by 30 by 21½ in.) and weighs 112 kg. (245 lb.). It requires a source of 60 cycle alternating current preferably at 115 volts, but is equipped with a voltage control which provides for the adjustment of line voltages to the desired 115 volt level. It draws 1,000 watts.

The Council obtained evidence indicating that the apparatus gave satisfactory results in operation such as transurethral prostatic resection. The surgeon is expected to have sufficient practice in the management of the two currents; tube-generated currents being generally inadequate for the control of hemorrhage, the proper admixture of spark gap currents was considered essential to reduce the danger of postoperative bleeding. The Council on Physical Medicine and Rehabilitation voted to include the Birtcher Electrosurgical Unit 799-H in its list of accepted devices.

SPECIAL FORMULA CRURICAST BANDAGE ACCEPTED

Manufacturer: E. K. Demmel Co., Inc., 59-11 67th Ave., Brooklyn 27.

The Cruricast Bandages are gauze bandages impregnated with a zinc gelatin paste, prepared in the form of a moist roller bandage of a 10-yard (914 cm.) standard length, wrapped in two sheets of waxed paper, and packed individually or by the dozen in sealed containers. The package of the 3-inch width (76 mm.) weighs 5¾ oz. (163 gm.); the 4-inch width (102 mm.) weighs 8 oz. (223 gm.). These bandages are used like Unna's paste boot in the treatment of circulatory disorders of the legs. Detailed comments on this point will be found in the announcement of acceptance of the regular Cruricast Bandage *J. A. M. A.* **118**:456 (Feb. 7) 1942. The Special Formula contains less glycerin, more gelatin, and more kaolin. This is claimed to be advantageous in hot, humid weather, when the unmodified Unna's paste is likely to remain moist and to soil the patient's clothes.

Evidence obtained by the Council indicated that this bandage had the advantage claimed for it. The Council on Physical Medicine and Rehabilitation voted to include the Special Formula Cruricast Bandage in its list of accepted devices.

LECTRON-O-SCOPE ACCEPTED

Manufacturer: Electronic Stethoscope Corporation, 1316 Sherman Ave., Evanston, Ill.

The Lectron-o-Scope is an electrical device that can be substituted for the bell of an ordinary stethoscope in order to amplify the sounds in auscultation.

For operation it requires a 1.25-volt A battery and 22-volt B battery. It weighs 225 gm. (8 oz.) and measures 5 cm. (diameter) by 14 cm. (2 by 5½ in.). Packed for shipment it weighs 450 gm. (1 lb.). The foreign shipping weight is 900 gm.

Lectron-o-Scope

The instrument was investigated for the Council. The investigator reported that it was satisfactory and pointed out that sounds were amplified that were seldom heard through the conventional stethoscope, especially by hard of hearing physicians. Thus, experience in the use of the Lectron-o-Scope is necessary in order to identify the amplified heart sounds. The Council on Physical Medicine and Rehabilitation voted to include the Lectron-o-Scope in its list of accepted devices.

TELEX HEARING AID, MODEL 300-B, ACCEPTED

Manufacturer: Telex, Inc., Telex Park, Minneapolis 1.

The Telex Hearing Aid, Model 300-B, is a conventional electric instrument, unusual mainly in its shape, which resembles that of a large fountain pen with a large clothing clip that carries the microphone. It also dispenses with the tone-control found on many other instruments. It measures 142 mm. in length and 17 mm. in diameter; the microphone measures 24 by 24 mm. Without batteries, cord, or receiver it weighs 83 gm. The batteries add 106 gm. and the cord and receiver add 10 gm.

Telex Hearing Aid, Model 300-B

Evidence from sources acceptable to the Council showed that this instrument was well constructed and performed as represented by the manufacturer. The Council on Physical Medicine and Rehabilitation voted to include the Telex Hearing Aid, Model 300-B, in its list of accepted devices.

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RESPIRATORY PROBLEMS OF BARBITURATE POISONING

A high mortality rate has been accepted by many as inevitable in severe barbiturate poisoning. Analeptics such as pentylenetetrazole (metrazol®) and picrotoxin are usually given in heroic doses to arouse the victim. A recent monograph [1] by Nilsson of Sweden challenges both these concepts.

He compares the severe depression of barbiturate overdosage to the similar state of profound surgical anesthesia. The gravest dangers in anesthesia are drug overdosage and lack of oxygen. Overdosage causes respiratory depression and hence suboxygenation. Overdosage of depressants also brings on hypoxia by a mechanism that is often neglected outside the operating room, namely, airway obstruction from the relaxed tongue and throat muscles. The loud stertor of any deeply unconscious patient is the measure of the obstruction that prevents the proper ingress of oxygen.

From the anesthesiologist's point of view, there is little to choose between deep anesthetic depression and that of barbiturate overdosage. In both, there is depression of respiration along with obstruction of the air passages by the relaxed throat muscles and tongue. Moreover, since the barbiturate poisoning victim is often untreated for hours, a long period of hypoxia has already damaged the brain, or at least interfered markedly with the efficiency of the respiratory and circulatory centers.

Anesthetic overdosage is always dealt with by first correcting any oxygen deficiency, and this entails better lung ventilation. Improvement of the airway and maintenance of a clear airway are primary. When the vital cerebral and myocardial tissues are receiving adequate oxygen, the overdosage is no longer an immediate hazard and can be corrected deliberately and without undue haste. Nilsson reasons that equally close attention to respiration is the clue to better results in treatment of barbiturate poisoning. His series of cases bear this out. In 176 instances of barbiturate poisoning, the condition was severe in 71 patients who had been unconscious more than 24 hours.

Therapy was centered on maintenance of free (i. e., noiseless) pulmonary ventilation. Frequent change of posture, artificial pharyngeal airways, tracheal tubes, and tracheotomy were employed. Oxygen therapy was easier to accomplish and much more effective when applied through freely open air passages. Shock was prevented by appropriate fluid therapy. No analeptics were used. The mortality rate in the patients with severe conditions was only 4.2%, and death occurred in only 2.3% of the 129 who had been unconscious at some time. In other series of cases in which analeptics were the mainstay of treatment, much poorer results were reported. From both American and European centers, mortality rates in excess of 15% seem to be the rule in severe cases.

Nilsson demonstrates that analeptics increase the oxygen demand in all tissues, thus leaving relatively less for the cerebral circulation. Therefore, he does not use them. The best argument for omitting them seems to be that they are not needed when oxygen reaches the circulation freely.

What effect Nilsson's report may have on current practices remains to be seen. Obviously, additional work is in order. However, even now there seem to be sufficient data to precipitate some very interesting arguments in this field.

RADIOACTIVE-IODINE-INDUCED HYPOTHYROIDISM IN THE TREATMENT OF CARDIAC PATIENTS

The physiologic relationship between the demands of metabolism and the supply of blood by the heart suggested that production of artificial hypothyroidism in a patient suffering from chronic heart disease might result in definite clinical improvement. This was supported by the fact that patients with thyrocardiac disorders were definitely improved by subtotal thyroidectomy. Blumgart and his associates [1] proposed, in 1933, total ablation of the normal thyroid for the relief of intractable heart disease. Clark and his associates [2] reported on 21 cardiac patients subjected to total ablation of the thyroid gland for the relief of congestive failure and angina pectoris. They felt that the operation was worth while in one-fourth of the patients. In Berlin's [3] series of 90 patients subjected to total thyroidectomy for the relief of intractable heart disease, 70% showed marked or moderate improvement. From a survey of literature and inquiries Parsons and Purks [4] analyzed the results of total thyroidectomy in 362 patients. Of the 229 patients with congestive heart failure, 64% showed excellent results and the remainder only slight or no improvement; of 133 patients with angina pectoris, 56% had excellent results, 28% moderate improvement and 16% no improvement.

Blumgart [5] points out, in a recent publication, that the operation carries a considerable surgical mortality rate

1. Nilsson, E.: On Treatment of Barbiturate Poisoning, Acta med. Scandinav., 1951, supp. 253.

1. Blumgart, H. L.; Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris: Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity, Arch. Int. Med. **51**: 866 (June) 1933.

2. Clark, R. J.; Means, J. H., and Sprague, H. B.: Total Thyroidectomy for Heart Disease: Experiences with Twenty-One Patients at the Massachusetts General Hospital, New England J. Med. **214**: 277 (Feb. 13) 1936.

3. Berlin, D. D.: Total Thyroidectomy for Intractable Heart Disease: Summary of Two and One-Half Years' Surgical Experience, J. A. M. A. **105**: 1104 (Oct. 5) 1935.

4. Parsons, W. H., and Purks, W. K.: Total Thyroidectomy for Heart Disease, Ann. Surg. **105**: 722, 1937.

5. Blumgart, H. L.; Freedberg, A. S., and Kurland, G. S.: Treatment of Incapacitated Euthyroid Cardiac Patients by Producing Hypothyroidism with Radioactive Iodine, New England J. Med. **245**: 83 (July 19) 1951.

and hazard of parathyroid and recurrent laryngeal nerve complications. He administered radioactive iodine, I^{131}, to induce hypometabolism. Patients were given tracer doses of 100 to 150 μc. The uptake of I^{131} by the thyroid was measured by the direct counting technic. The initial dose was calculated to deliver approximately 30,000 to 50,000 roentgen equivalents. About two-thirds of the 37 patients in this group experienced mild to moderate thyroiditis lasting one to 10 days. Signs of hypometabolism usually became manifest five weeks to six months after an adequate dose of I^{131}. When hypometabolism did not develop within several months, additional doses after preliminary tracer doses were given.

Symptoms of myxedema were usually associated with high levels of serum cholesterol and a corresponding improvement in the cardiac state. In a follow-up of 23 of the patients in hypometabolic state over a period of 7 to 26 months, no serious toxic or untoward reactions were observed. In one-third of the patients there was remarkable improvement; in one-third there was definite and significant improvement; in another third there was no significant improvement. Small doses of thyroid were given after the induction of myxedema to keep the patient comfortable. Patients suited for this type of therapy are those whose disease has been relatively stationary or only slightly progressive. These patients should show evidence of some cardiac reserve, such as ability to lose the signs of congestive failure on bed rest or with the use of diuretics and digitalis. The basal metabolic rate should be above —10%. This form of therapy may find a place in a carefully selected class of patients.

METABOLIC FATE OF THIOPENTAL SODIUM

Thiopental, administered as the sodium salt, has been widely used in clinical anesthesia since its introduction in 1935. However, until recently, little was known of its metabolic fate, owing largely to a lack of specific, sensitive micro-methods for the determination of the drug and its degradation products in biological material.

The very short action of thiopental and its rapid disappearance from the blood stream, coupled with the negligible amounts excreted in the urine or stored in various organs of the body, led to the concept of rapid breakdown in the body.[1] While earlier reports were somewhat contradictory, Shideman, Kelly, and Adams, in 1947, presented evidence that the liver was an important site of detoxification.[2] These authors found that the duration of thiopental anesthesia was significantly prolonged in mice after carbon tetrachloride liver damage and in rats with Eck fistulas or after subtotal hepatectomy. They also reported in vitro degradation of thiopental by rat liver slices and mince. Similar activity has been reported by Dorfman and Goldbaum [3] using rabbit liver and kidney slices and brain brei and by Gould and Shideman [4] using cell-free preparations of rat liver.

Recently, Brodie and his associates [5] described specific spectrophotometric methods for the determination of thiopental and thiopental carboxylic acid, which they identified as a metabolite of thiopental. Using these methods, they have shown that in human subjects some 0.3% of the administered dose of thiopental is excreted as thiopental and 10% to 25% as the carboxylic acid derivative. After intravenous administration, the plasma concentration of thiopental fell rapidly in the first 30 minutes and then more slowly. The investigators interpreted the sharp decline to a shift of thiopental from plasma to tissues rather than to rapid destruction of the drug. The slow decline represented the rate of metabolic breakdown as the equilibrium between plasma and tissues became established. When relatively large doses of the drug were administered (1 to 6 gm.) to human subjects, prolonged periods of unconsciousness (one to six hours) resulted. The rate of decline of thiopental levels observed after one or two hours following administration was only about 15% per hour.

Brodie and his associates found that in the dog the disappearance of thiopental from the blood was much slower than in man and that only traces of thiopental carboxylic acid were found in the dog's urine. Apparently the slower rate of degradation of thiopental in this species permits complete transformation of the small amounts of the carboxylic acid metabolite present in the body at any time. Thiopental tissue distribution studies in dogs indicated that, in most tissues, the concentration of thiopental was about equal to that of the plasma but was considerably higher than in the plasma water, indicating some localization of the drug. Of great interest, however, was the fact that, when fat deposits such as omentum and perirenal and lumbodorsal fat were analyzed for total lipid and thiopental, the pentothal concentrations, expressed in terms of total lipid, were six to twelve times greater than those of plasma. Further calculations indicated that the major portion of the administered thiopental was ultimately deposited in fat.

The development of thiopental labeled with radioactive sulfur offers a sensitive analytic tool for distribution and excretion studies, provided suitable extraction methods are employed to separate the drug and its degradation products. In studies with S^{35} labeled thiopental, Brodie's observations on the significant uptake of thiopental in fat were confirmed by Bollman, Brooks, Flock, and Lundy [6] and by Taylor, Richards, and Tabern.[7] Additional chromatographic studies with labeled thiopental have led Tabern, Taylor, and Gleason [8] to suggest that thiopental may be degraded in the body by side chain oxidation, by enzymatic removal of the sulfur or possibly by splitting of the malonylthiourea ring with the ultimate liberation of hydrogen sulfide and ammonia.

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1. Jailer, J. W., and Goldbaum, L. R.: Studies on the Plasma Concentration and Tissue Distribution of Sodium Pentothal (Sodium Ethyl [1-Methylbutyl] Thiobarbiturate), J. Lab. & Clin. Med. **31**: 1344, 1946.
2. Shideman, F. E.; Kelly, A. R., and Adams, B. J.: The Role of the Liver in the Detoxication of Thiopental (Pentothal) and Two Other Thiobarbiturates, J. Pharmacol. & Exper. Therap. **91**: 331, 1947.
3. Dorfman, A., and Goldbaum, L. R.: Detoxification of Barbiturates, J. Pharmacol. & Exper. Therap. **90**: 330, 1947.
4. Gould, T. C., and Shideman, F. E.: Further Studies on in Vitro Metabolism of Thiopental, Federation Proc. **10**: 299, 1951.
5. Brodie, B. B.; Mark, L. C.; Papper, E. M.; Lief, P. A.; Berstein, E., and Rovenstine, E. A.: The Fate of Thiopental in Man and a Method for Its Estimation in Biological Material, J. Pharmacol. & Exper. Therap. **98**: 85, 1950.
6. Bollman, J. L.; Brooks, L. M.; Flock, E. V., and Lundy, J. S.: Tissue Distribution with Time After Single Intravenous Administration of Pentothal Sodium (Sodium Ethyl [1-Methylbutyl] and Pentothal S35 Thiobarbiturate), Anesthesiology **11**: 1, 1950.
7. Taylor, J. D.; Richards, R. K., and Tabern, D. L.: Distribution of Radioactive S35 of Thiopental (Pentothal) in the Rabbit and the Cat, Current Res. in Anesth. & Analg. **29**: 101, 1950.
8. Tabern, D. L.; Taylor, J. D., and Gleason, G. I.: Radioisotopes in Pharmaceutical and Medical Studies, Nucleonics **1**: 40, 1950.

Further information on the metabolic oxidation of thiopental is presented by the work of Giarman, Flick, and White.[9] Prompted by the report by Richert, Vanderlinde, and Westerfeld [10] that tetraethylthiuram disulfide (antabuse®) inhibits rat xanthine oxidase, these workers studied the effect of tetraethylthiuram disulfide on thiopental anesthesia in the mouse. They found that, when a group of mice were given, by intravenous route, 30 mg. of thiopental per kilogram of body weight, the mean duration of anesthesia was 4.7 minutes. However, if the mice were premedicated for three days with an oral daily dose of 25 mg. of tetraethylthiuram disulfide, the mean duration of anesthesia was 256.2 minutes, with no observable postanesthetic toxic effects. Richert, Vanderlinde, and Westerfeld concluded that xanthine oxidase consisted of two independent enzymatic activities, a dehydrogenase activity and an oxidase activity, and that only the latter was inhibited by tetraethylthiuram disulfide. Giarman and his co-workers suggest that the premedication period with tetraethylthiuram disulfide is necessary in order to allow all the dehydrogenase to be reduced. As a practical corollary, the authors suggest that thiopental be administered with caution to patients undergoing treatment with tetraethylthiuram disulfide.

ENCEPHALOMYELITIS VIRUS IN WILD BIRDS

Howitt [1] and her associates of the United States Public Health Service, Atlanta, Ga., report the isolation of encephalomyelitis virus from the blood of nestling wild birds in Colorado. Nestlings from over 600 nests were tested. Birds studied included pigeons, swallows, sparrows, magpies, and blackbirds. On three occasions, intracerebral inoculations of 0.02 cc. of heart blood from these nestlings into 12 to 14-day-old white mice produced symptoms of encephalitis or death in two to five days. The causative agent was fully identified as western equine encephalomyelitis virus.

The Atlanta epidemiologists also tested 78 lots of mites found in the nests of these birds.[2] The virus of western equine encephalomyelitis was obtained from one lot only. The virus-positive mites were taken from the nest of an English sparrow, on a farm where a human case of encephalitis had recently occurred. Antibodies neutralizing western equine encephalomyelitis virus were demonstrated in the serum of this patient.

Other members of the Atlanta group [3] isolated eastern equine encephalomyelitis virus from the blood of a purple grackle shot in Louisiana. Mosquitoes were collected by a light trap [4] near the place where this bird was shot. Eastern equine encephalomyelitis virus was isolated from two specimens of Culiseta melanura thus collected. These studies indicate that birds may act as natural reservoirs of encephalomyelitis viruses.

UTILIZATION OF CARBON DIOXIDE BY THE ANIMAL ORGANISM

Until nearly a decade ago, carbon dioxide, insofar as the animal organism was concerned, was considered a waste product of cellular oxidations. The utilization of carbon dioxide for the synthesis of cellular constituents was thought to be limited to plants. The advent of isotopes as tracers for the study of metabolic processes in the animal body, however, has radically altered this concept. As early as 1942, the then surprising observation was made by a group of Harvard investigators [1] that carbon dioxide from $NaHC^{11}O_3$ was utilized in the synthesis of glycogen by the liver of the rat. Subsequent studies [2] have verified this unique finding and, indeed, have shown that carbon dioxide may be utilized by the animal organism in the synthesis of a number of other compounds of physiological importance.

The foregoing revolutionary observations at once stimulated interest in the mechanism involved in carbon dioxide fixation by animal tissues. As is brought out in a recent review of the biological mechanisms of carboxylation and decarboxylation,[3] the "citric acid cycle," originally proposed as a mechanism for the degradation of metabolites with the release of carbon dioxide, appears to be involved in the utilization of carbon dioxide by the animal, "heterotrophic," organism. There is reviewed evidence which shows that carbon dioxide fixation by heterotrophic cells occurs with the formation of such intermediates as citric, malic, and perhaps other acids of the citric acid cycle. The inference, therefore, is that the citric acid cycle is an important mechanism for carbon dioxide fixation. Certain enzymes and other necessary substances for this process have also been demonstrated. Another point of great interest is that plant tissues have also been shown to contain many of these same organic acids and enzymes. This finding has led to a current view that the utilization of carbon dioxide for photosynthesis in autotrophic, "plant," cells is basically through a reversal of the citric acid or a similar cycle which is used primarily for the degradation of metabolites with the release of carbon dioxide and energy by animal cells. Whether or not subsequent investigations prove this intriguing concept correct, the importance of the dicarboxylic and tricarboxylic acids, for the degradation of metabolites with the release of carbon dioxide and energy and also for the utilization of carbon dioxide in the synthesis of essential compounds in animal tissues, appears to be well established.

9. Giarman, N. J.; Flick, F. H., and White, J. M.: Prolongation of Thiopental Anesthesia in the Mouse by Premedication with Tetraethylthiuram Disulfide ("Antabuse"), Science **114**: 35, 1951.

10. Richert, D. A.; Vanderlinde, R., and Westerfeld, W. W.: The Composition of Rat Liver Xanthine Oxidase and Its Inhibition by Antabuse, J. Biol. Chem. **186**: 261, 1950.

1. Sooter, C. A.; Howitt, B. F.; Gorrie, R., and Corkburn, I. A.: Encephalitis in Midwest: IV. Western Equine Encephalitis Virus Recovered from Nestling Wild Birds in Nature, Proc. Soc. Exper. Biol. & Med. **77**: 393 (July) 1951.

2. Miles, V. I.; Howitt, B. F.; Gorrie, R., and Corkburn, I. A.: Encephalitis in Midwest: V. Western Equine Encephalomyelitis Virus Recovered from Mites Dermanyssus Americanus Ewing, Proc. Soc. Exper. Biol. & Med. **77**:395 (July) 1951.

3. Kissling, R. E.; Rubin, H.; Chamberlain, R. W., and Edison, M. E.: Recovery of Virus of Eastern Equine Encephalomyelitis from Blood of a Purple Grackle, Proc. Soc. Exper. Biol. & Med. **77**:398 (July) 1951.

4. Chamberlain, R. W.; Rubin, H.; Kissling, R. E., and Edison, M. D.: Recovery of Virus of Eastern Equine Encephalomyelitis from a Mosquito, Culiseta melanura (Coquillett), Proc. Soc. Exper. Biol. & Med. **77**:396 (July) 1951.

1. Vennesland, B.; Solomon, A. K.; Buchanan, J. M., and Hastings, A. B.: Glycogen Formation from Glucose in the Presence of Radioactive Carbon Dioxide, J. Biol. Chem. **142**: 379 (Jan.) 1942.

2. Wood, H. G.: The Fixation of Carbon Dioxide and the Interrelationships of the Tricarboxylic Acid Cycle, Physiol. Rev. **26**: 198 (April) 1946.

3. Ochoa, S.: Biological Mechanisms of Carboxylation and Decarboxylation, Physiol. Rev. **31**: 56, 1951.

THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

One of the newest of A. M. A.'s Councils, yet one of the most important in this mobilization-conscious decade, is the Council on National Emergency Medical Service. This is the Council that advises, among other things, on procurement and allotment of physicians for the armed forces. It also works closely with the Federal Civil Defense Administration on the medical aspects of civil defense, and studies medical experiences in such disasters as the Kansas flood.

The Council made its first appearance as the Committee on Military Medicine in 1945. It was organized at that time to try to improve the status of medicine in the armed forces. In 1946 its name was changed to the Committee on National Emergency Medical Service to reflect more clearly the widening scope of its activity, and then in 1947 it was elevated to Council status.

As the nation has mobilized, the work of the Council has increased. Because of the large occupation forces in Germany and Japan, and particularly because of the Korean conflict, the utilization of medical personnel in the armed forces had to be put back on a semi-wartime basis. The Council supported the draft of physicians as the most equitable means of meeting the increased military need for medical officers and has continued to work closely with the three armed forces Surgeons General and with the Armed Forces Medical Policy Council of the Department of Defense.

One of the signal achievements of the Council was the early establishment of civilian medical advisory committees at top government levels to represent the interests of the civilian population in the allotment of medical manpower. These include advisory committees to the National Security Resources Board, the Selective Service System, and the Secretary of Defense.

On behalf of the profession, the Council has bent its efforts toward four particular goals: (1) to prevent a repetition of the medical over-staffing which occurred in certain areas during World War II; (2) to curtail the utilization of medical personnel on nonprofessional assignments; (3) to facilitate and increase the efficiency of the administration of the doctor draft law; and (4) to effect a timely and orderly system of recall and rotation of medical reservists. Reports from both individual physicians and military leaders indicate that there has been marked improvement in the recruitment and utilization of medical personnel in the armed forces. In addition, all information from the Korean theater indicates that the medical care being provided for our troops is superior to that furnished during any other period in our nation's history. The A. M. A.'s Council can certainly take partial credit for this improved situation in military medicine.

Continuing effort on the part of the Council also has contributed to the adoption of two important policies on the part of the federal government. One is the transferring of permanently disabled service personnel to Veterans Administration hospitals and domiciliary centers. This policy has resulted in a more efficient use of veterans facilities and a reduction in the need for additional military medical installations.

The second policy is to use civilian physicians with reserve commissions to perform induction and periodic reserve physical examinations. This procedure reduces the number of doctors required in the armed forces and permits the individual physician to earn point credits under the provisions of Public Law 810.

The Council has also made recommendations concerning the Universal Military Training Program and has opposed proposals to extend medical benefits to dependents of service personnel without regard to need or to the availability of private facilities.

A growing proportion of the Council's activity has been in the field of civil defense. Because of this interest on the part of the Council and on the part of a number of individual physicians, it is a well-recognized fact that medical planning is far ahead of most other phases of civil defense.

The Council stimulated the organization of Emergency Medical Service Committees in all state medical societies and has kept them informed of developments, literature, and plans in the civil defense field. One means by which this is accomplished is a monthly informational news letter sent out by the Council office at A. M. A. headquarters. It goes to over 500 physicians in all the states and territories.

The Council has also published three pamphlets on planning and organizing for radiological defense and is currently presenting a series of 10 articles on the medical aspects of civil defense in THE JOURNAL. Later these will be reproduced and distributed in booklet form.

To further stimulate medical civil defense planning on the state level, the Council next month will conduct a National Conference on Medical Civil Defense. This conference, which is to be held November 9 and 10 in Chicago, will be co-sponsored by the American Hospital Association and the Association of State and Territorial Health Officers.

Three representatives are being invited from each state—a representative from the medical society, one from the state health department, and one from the state hospital association. The purpose of the conference is to inform these leaders on planning for civil defense and, also, to encourage them to coordinate their activities in this field. Coordination is especially important, for in case of a disaster all medical facilities will be desperately needed.

An outstanding program has been developed for this conference, including top officials from all the sponsoring organizations and those physicians who have been most active in developing medical defense programs. I personally urge every state society to be represented at this vital meeting.

It is unfortunate but true that our concern for the welfare of our patients must today go beyond our own personal efforts to cure their ills. We would be neglecting our duty if we failed to prepare as a profession for the disaster that may come. The work of the A. M. A.'s Council on National Emergency Medical Service, therefore, is of the highest importance and deserves the support and interest of every physician.

JOHN W. CLINE, M.D., San Francisco.

MEDICAL NEWS

ARIZONA

Mental Health Director Resigns.—Dr. Edith E. Lord, who became Arizona's first director of mental health two years ago, resigned Sept. 1 from the state health department to accept a position with the Veterans Administration in New York. Now serving as acting director of the state's Mental Health Division is William E. Macomber, clinical psychologist, formerly with the Amphitheater Schools in Tucson. Dr. Lord is now director in charge of the program for Veterans Administration doctoral degree candidates in clinical psychology at New York and Columbia universities. She will work primarily with neuropsychiatric hospitals and clinics in the New York City area. Prior to coming to Arizona, she was with the Territorial Bureau of Mental Hygiene in Hawaii.

CALIFORNIA

England's Mellanby to Lecture.—Sir Edward Mellanby, emeritus professor of physiology, Royal Institute, and emeritus professor of pharmacology, Sheffield University in England, will address the San Francisco Medical Society at 8:15 p. m. Oct. 30 at society headquarters on "Nutrition and Disease."

State General Practitioners Meeting.—Postgraduate education will take the form of a scientific assembly at the Hotel del Coronado, Coronado, San Diego, Nov. 5-7 when members of the California Academy of General Practice convene for their third state meeting. Visiting lecturers include Dr. Theodore K. Lawless, Chicago dermatologist; Dr. Leonard Scheele, Surgeon General, U. S. Public Health Service, and Dr. George F. Bond of Bat Cave, N. C.

COLORADO

Memorial to Dr. Ward.—A main boulevard at Army Tripler General Hospital in Hawaii has been named in honor of the late Col. Donald Meyers Ward, a former Denver physician, who was on the staff of Fitizsimons General Hospital. Colonel Ward died on Nov. 20, 1944, while serving as island surgeon on Guadalcanal.

University Appointment.—Dr. George Milton Shy, lecturer in neurology at McGill University in Montreal, Canada, has been appointed an assistant professor of neurology in the department of medicine at the University of Colorado School of Medicine, Denver. Prior to going to McGill University, where he remained for three years, Dr. Shy taught at Oregon State. He has spent two years abroad in special study at the National Hospital in London, England.

CONNECTICUT

State Department Reorganized.—The Connecticut State Department of Health has been reorganized into four major service sections to expedite the work and render more effective public service. The four sections are administrative services under the direct supervision of the commissioner, community health services under Dr. Martha L. Clifford, medical services under Dr. Harold S. Barrett, and environmental health services under Dr. Edwin Cameron. No changes in directors and chiefs of the bureaus and divisions are contemplated.

Dr. Fulton Will Be Exchange Professor.—Dr. John F. Fulton, Sterling Professor of the History of Medicine at Yale University, New Haven, will serve as exchange professor of physiology at Belgium's University of Louvain and will also deliver a Sherrington Lecture at the University of Liverpool, England. He will be in residency at the University of Louvain under the sponsorship of the Belgian Francqui Foundation. The Sherrington Lectures were founded in honor of Sir Charles Sherrington, professor of physiology at Liverpool from 1895 to 1913, under whom Dr. Fulton was a student at Oxford University from 1921 to 1925.

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education and public health. Programs should be received at least three weeks before the date of meeting.

ILLINOIS

Ophthalmia Prophylaxis in the Newborn.—The Illinois Department of Public Health recently declared it "will continue to accept 1% silver nitrate solution as the only approved drug for the prophylaxis of ophthalmia neonatorum until it is convinced that penicillin solutions (or any other antibiotic) can be used throughout the state in both home and hospital with the same degree of safety and effectiveness as silver nitrate." This statement was issued by the department in its weekly bulletin because of pressure from numerous sources advocating the use of penicillin solutions in the prevention of ophthalmia neonatorum. Illinois statutes require prophylactic treatment of the eyes of every newborn baby within an hour after birth. Explaining its continued preference for silver nitrate, the department said this agent is a time-proven effective agent, is safe to use, requires only a single application, and is very stable when kept in a wax ampule. The National Society for the Prevention of Blindness has expressed reservations on the adoption of penicillin for treatment of babies' eyes. These came after the society made a careful study of research on the antibiotic treatment conducted at Johns Hopkins Hospital, Cornell University Medical School, the University of Iowa, the University of Tennessee Medical School, Ohio State University, and in Trenton, N. J.

Chicago

Society News.—Newly elected officers of the Chicago Society of Allergy for 1951-52 include Dr. Theron G. Randolph, president, Dr. Milton M. Mosko, president-elect, and Dr. Abraham L. Aaronson, secretary-treasurer.

Fraternity Lectureship.—The Third Annual Phi Delta Epsilon Fraternity Lectureship honoring Drs. Isaac A. Abt, Julius H. Hess, and John J. Sheinin was held Oct. 22-24. The guest lecturer was Dr. William Dameshek, professor of clinical medicine at Tufts College Medical School, Boston. The lectures were as follows:

Spleen and Hypersplenism, Oct. 22 at 8 p. m., Kling Auditorium, Mount Sinai Hospital.
"Idiopathic" Thrombocytopenic Purpura, Oct. 23 at 4 p. m., Thorne Hall, Northwestern University Chicago campus.
Principles of Hemolytic Anemia, Oct. 24 at 1 p. m., Room 221, University of Illinois School of Medicine.

The annual banquet of the lectureship was held at the Furniture Club, 666 Lake Shore Drive, Oct. 23 at 6:30 p. m. The speaker was Dr. Austin Smith, Chicago, Editor of THE JOURNAL.

Tuberculosis Society.—The Chicago Tuberculosis Society will meet Oct. 29 at the Institute of Medicine of Chicago at 8 p. m. Dr. Otto L. Bettag, Pontiac, Ill., will give the president's address on "Facts and Foolishness—Tuberculosis." Other papers to be given include the following:

Linden J. Wallner, J. Robert Thompson, and Meyer R. Lichtenstein, Clinical and Histopathological Study of Cortisone and ACTH in Tuberculosis: Failure to Affect Mucosal Lesions.
Jakub G. Schlichter, Sarcoidosis Complicating Rheumatic Fever.
Aaron Keinigsberg, Pregnancy in Pulmonary Sarcoidosis: Report of Two Cases.

Armour Laboratories Appointments.—Dr. Marvin C. Ziporyn, once laboratory director at the U. S. Marine Hospital, Ft. Stanton, N. M., and a senior assistant surgeon in the United States Public Health Service, has been appointed assistant medical director of Armour Laboratories. Dr. Emil A. Fullgrabe has been named regional medical director for the southwestern region in Dallas, Texas. Dr. Fullgrabe has served as director of laboratories at St. Joseph Mercy Hospital, Sioux City, Iowa, and as associate professor of pathology at the University of South Dakota in Vermillion.

INDIANA

Narcotic Violation.—Dr. James Maurice Hicks Jr. pleaded guilty at Fort Wayne to a violation of the federal narcotic law and on Sept. 7 was placed on probation for three years.

Grants to Riley Hospital.—Grants totaling $68,267 for research and equipment in the laboratories of the James Whitcomb Riley Hospital for Children at the Indiana University Medical Center, Indianapolis, have been announced by the Riley Memorial Association. The new research and service laboratories, one in biochemistry for the study of children's diseases from the chemical standpoint and the other in orthopedic surgery, will be established under the new grants, and a number of research projects will be instituted.

MAINE

Maine Clinical Session.—A clinical session of the Maine Medical Association will be held Oct. 28-30 at the Central Maine General Hospital and DeWitt Hotel, Lewiston. At the evening meeting there will be a symposium on malignancies of the chest, the participants being Dr. Harry S. N. Greene, New Haven, Conn.; Dr. Richard H. Overholt, Brookline, Mass., and two other visiting clinicians.

Pediatric Institute.—More than 70 physicians attended a pediatric institute for general practitioners at the Eastern Maine General Hospital, Bangor, Sept. 21. The institute was sponsored by the Division of Maternal and Child Health of the Maine Department of Health and Welfare and was endorsed by the Maine Medical Association. Speakers were from the Children's Medical Center in Boston. Dr. Louis K. Diamond spoke on "Treatable Anemias of Infancy and Childhood"; Dr. Harry Shwachman on "Drug Dosage for Children"; and Dr. Alexander Nadas on "Congenital Heart Disease—Its Treatment and Prognosis."

MASSACHUSETTS

A Diabetes Fair.—The New England Diabetes Association will hold a "Diabetes Fair" on Nov. 14 and 15 from 11 a. m. to 10 p. m. at Horticultural Hall, Boston, in connection with National Diabetes Week. The purpose is to stimulate interest in diabetes and help discover unknown diabetics. Dr. Harry Blotner, Boston, is chairman of the association's Committee on Public Education and Diabetes Detection. A program of interest to the public, social service workers, dieticians, medical students, and physicians has been arranged. There will be a variety of exhibits. Urine and blood sugar testing facilities will be available. On Wednesday evening at 8 p. m. a public meeting on diabetes will be held. The speakers will be Dr. Blotner, Dr. Frederick W. Williams, New York, editor of the *A. D. A. Forecast;* Dr. F. Gorham Brigham, Brookline, and Dr. Elliott P. Joslin, Boston.

Hospital Evening Lectures.—The House Officers' Association of the Boston City Hospital announces the following programs in its evening lecture series:

Oct. 30, The General-Adaptation-Syndrome, Hans Selye, Montreal, Canada.
Nov. 6, Iron Metabolism and the Pathogenesis of Iron Deficiency Anemia, Carl Moore, St. Louis.
Nov. 8, Blood Substitutes and Their Use in the Treatment of Shock, James V. Warren, Atlanta, Ga.
Nov. 20, Diabetic Acidosis, Edward Tolstoi, New York.
Nov. 27, Periodic Disease, Hobart A. Reimann, Philadelphia.

These programs will be held at 7 p. m. in the New Cheever Amphitheatre of the Dowling Building of Boston City Hospital. All interested persons are invited.

MICHIGAN

General Practice Lectures.—The Michigan Academy of General Practice in conjunction with the Wayne County group of the academy will hear the fifth series of lectures for general practitioners at Henry Ford Hospital, Nov. 7-8. This year the lectures are to be dedicated to the late Dr. Roy D. McClure, through whose cooperation the first of the lectures were held at the hospital.

MISSISSIPPI

Society News.—The semiannual meeting of the Delta Medical Society will be held in Greenville Oct. 10. Dr. William Milton Adams, Memphis, Tenn., will speak on the immediate treatment of burns.

State Society Employs Executive Secretary.—Mr. Rowland B. Kennedy of Clinton has been selected by the Mississippi State Medical Association as its executive secretary. Mr. Kennedy was formerly employed for more than three years as state programs director in the state department of the American Legion and served as managing editor of the state-wide newspaper *The Mississippi Veteran.* He had previously assisted in preparing and distributing favorable publicity for the establishment of the state's four year medical school in cooperation with the president of the state medical association.

NEW HAMPSHIRE

Society News.—Officers for the New Hampshire Pediatric Society for the year 1951 are Dr. Douglass W. Walker, Laconia, president, and Dr. William D. Penhale, Concord, secretary-treasurer.

Report of State Medical Meeting.—The New Hampshire Medical Society, meeting in Manchester Sept. 30-Oct. 2, installed Dr. B. Read Lewin, Claremont, as president. Other officers for the year are Dr. Joseph N. Friborg, Manchester, president-elect; Dr. Raymond H. Marcotte, Nashua, vice-president; Dr. Deering G. Smith, Nashua, secretary-treasurer and delegate to the American Medical Association, and Dr. Howard P. Sawyer, Brookfield, alternate delegate. The society passed the following resolution:

. . . the New Hampshire Medical Society believes that the requirements for approved schools of nursing in this state should be sufficiently high to ensure well-trained nurses. These requirements must be formulated to meet the conditions in New Hampshire and be reasonable so that they can be met by the hospitals in this state. The physicians of New Hampshire are interested in having an adequate supply of good nurses to care for their patients, and believe that every effort should be made by the various interested agencies, including the Board of Nurse Examiners, to achieve this result.

NEW YORK

Society News.—The Rochester Academy of Medicine will hear the following speakers at their meetings at 1441 East Avenue, 8:30 p. m.:

Nov. 13, Merrill C. Sosman, Boston, Cardiovascular Radiology.
Dec. 4, Robert R. Linton, Brookline, Mass., Surgical Treatment of Bleeding Esophageal Varices.

Medical Education Fund.—The Medical Society of the State of New York at its last meeting agreed to pledge the doctors of New York State to attempt to raise $250,000 in 1951 to provide financial aid to medical schools. To facilitate the collection of funds in the Medical Society of the County of New York, a special committee on funds for medical education has been set up with Dr. Alfred Hellman, former president of the society, serving as chairman.

Law-Science Course.—About 100 medical-legal men attended the Law-Science Course given with the cooperation of the New York Society of Medical Jurisprudence Sept. 4-8 at the Hotel Astor, New York, on Legal Medicine and Elements of Medico-Legal Litigation for Lawyers and Physicians Concerned with Personal Injury Litigation. Among the fifty lecturers were the following:

George T. Pack, Relation of Cancer to Trauma.
Milton Helpern, New York, The Postmortem Examination.
Wladimir G. Eliasberg, New York, Psychiatric Approach to the Adult Offender.
S. Philip Goodhart, New York, Medico-Legal Aspects of Malingering.
Frank R. Ferlaino, New York, Industrial and Liability Manifestations.
Howard J. Hutter, Huntington, N. Y., Pitfalls of X-Ray Diagnosis.
Solomon Fineman, New York, Pitfalls of X-Ray Diagnosis.
Leonard J. Goldwater, New York, Socio-Medico-Legal Aspects of Industrial Medicine.
George G. Deaver, New York, Tools and Procedures in Rehabilitation.
Mr. Edward T. Welch, Statute of Limitation in Medical Malpractice Actions.

New York City

New Child Health Director.—Dr. Harold Jacobziner, since 1948 chief of the school health services in the Bureau of School Health, has been named director of the Bureau of Child Health of the city department of health. Dr. Jacobziner, who has been on the staff of the department of health since 1931, replaces Dr. Samuel M. Wishik, who recently left the department.

Third Health Center Nearing Completion.—A cornerstone ceremony was held Sept. 21 for the new Jamaica District Health Center and Queens Borough Office of the Department of Health. The $1,250,000 structure, construction of which was begun in Aug. 1950, is expected to open next spring. The district center is the third in Queens, where eventually six such stations will be operated. Serving an area populated by 500,000 persons, the Jamaica Center will have clinics for tuberculosis, social hygiene, and dental and nutritional services.

Sydenham Hospital Acquired by City.—The city formally acquired title to the property of Sydenham Hospital on Aug. 4 for $1,050,000. Although the Board of Estimate authorized acquisition of the hospital through condemnation on July 17, 1950, the proceedings were not completed until a final court decree last July 30. The city took over operation of the private financially burdened institution on March 3, 1949. Although Sydenham is no longer a private voluntary hospital, it still provides facilities for the care of private and semiprivate patients with their own doctors in attendance. The hospital was built in 1926.

Dr. Ruggles to Give Salmon Lectures.—The Salmon Committee on Psychiatry and Mental Hygiene announces that Dr. Arthur Hiler Ruggles, Providence, R. I., will deliver this year's Thomas William Salmon Lectures at the New York Academy of Medicine. His subject will be "The Place and Scope of Psychotherapy," and the talks will be given Nov. 7, 14, and 20 at 8:30 p. m. Dr. Ruggles is a former president of the American Psychiatric Association and of the National Committee for Mental Health. During World War II he was consultant to the Secretary of War. He is at present general consultant to Butler Hospital, Providence, R. I., of which he was superintendent for 26 years, and special consultant to the Emma Pendleton Bradley Home in East Providence.

Lectures to the Laity.—"Society and Medicine" is the subject of the 1951-52 Lectures to the Laity, 17th series, to be presented by the New York Academy of Medicine Nov. 9 through Jan. 30 at academy headquarters. The program is as follows:

Nov. 9, The Linsly R. Williams Memorial Lecture, Sir James Spence, Newcastle-upon-Tyne, England, Disease and Its Local Setting.
Nov. 21, Ralph W. Gerard, Chicago, Biology of Ethics.
Dec. 5, Howard S. Liddell, Ph.D., New York, Anniversary Discourse of the New York Academy of Medicine, The Natural History of Neurotic Behavior.
Dec. 19, Theodore H. Ingalls, Boston, Environment in Heredity.
Jan. 9, Milton J. E. Senn, New Haven, Conn., The Art and Science of Growing Up.
Jan. 30, Russell M. Wilder, Bethesda, Md., The George R. Siedenberg Memorial Lecture, The Evolution of Nutrition.

Personals.—Dr. Frederick S. Reiss, associate clinical professor of dermatology and syphilology, New York University Postgraduate Medical School, has been elected a corresponding member of the Austrian Dermatological Society.——Dr. Walter J. Lear of Arlington, Va., and Mr. Harvey Schoenfeld of Brooklyn have been named assistant directors of Montefiore Hospital for Chronic Diseases.——Dr. Francis B. Berry, professor of clinical surgery, College of Physicians and Surgeons, Columbia University, has been appointed a civilian member of the committee on medical sciences, Research and Development Board, Department of Defense. Dr. Berry succeeds Dr. Isador Ravdin, University of Pennsylvania, Philadelphia, who resigned when he became a member of the Armed Forces Medical Policy Council. ——Dr. George T. Pack spoke before the First Argentinian Cancer Congress in Buenos Aires, on "Gastric Cancer" and "Malignant Melanoma."——Dr. Arthur A. Knapp spoke before the British Medical Association, West Indies Branch, meeting in Trinidad, Sept. 5. His subject was "Uveitis and Retinitis Pigmentosa: Cure and Treatment."

NORTH CAROLINA

Narcotic Violation.—Dr. Frederick D. Quick, Rockingham, pleaded guilty to an indictment charging a violation of the federal narcotic law in the District Court at Rockingham, and on Sept. 11 his sentence of two years was suspended and he was placed on probation for a like period. He was also fined the sum of $500.

State to Fight Diphtheria.—Following the announcement that in 1950 North Carolina led the entire nation in the rate of diphtheria cases reported, Dr. John W. R. Norton, state health officer, called on health departments throughout the state to step up the campaign against the disease. He cited figures recently released by the United States Public Health Service showing that last year the state's case rate was 12.4 for each 100,000 persons as compared with a national rate of 3.9. Among all the 48 states, 10 had a case rate last year of one or less. Reports of diphtheria cases in North Carolina, received by the state board of health through August of this year, showed a total of 174 cases. The total for 1950, as reported, was 500 with 27 diphtheria deaths. Immunization against diphtheria and whooping cough is mandatory, by law, in North Carolina.

OHIO

Health and Safety Center.—Columbus will begin construction about Nov. 1 on a new City Health and Safety Center, which is to cost over a million dollars. All five health agencies of the county will have offices in the building, which is to be located in the Civic Center. Clinics for tuberculosis, venereal disease, maternal and child health, and dental and mental hygiene will also be located there. Space has been provided for the Columbus Cancer Society and an auditorium for use as a food handler classroom and other health education lectures.

Course in Diseases of the Chest.—Mount Sinai Hospital, Cleveland, will give a postgraduate course on Recent Advances in Diseases of the Chest on Monday nights, with one exception, Nov. 5-Dec. 20 at 8 p. m. The lectures will cover roentgenologic anatomy of the broncho-pulmonary segments, acute pneumonias, pulmonary and bronchial suppurative disease, intrathoracic tumors, tuberculosis, and occupational pulmonary disease. The final lecture on Thursday, Dec. 20, will be open to the public. Dr. Sol R. Rosenthal, Chicago, will speak on "BCG Vaccination in Tuberculosis."

OKLAHOMA

Fall Clinical Conference.—This conference of the Oklahoma City Clinical Society will be held Oct. 29-Nov. 1 with headquarters at the Oklahoma Biltmore Hotel, Oklahoma City. Visiting speakers include the following:

George Crile Jr., Cleveland, Present Status of the Treatment of the Thyroid Gland.
Lemuel W. Diggs, Memphis, Selection of Laboratory Tests Used in General Practice.
F. Bayard Carter, Durham, N. C., Vaginitis.
Ashton L. Welsh, Cincinnati, Vesicular and Bullous Diseases.
N. Frederick Hicken, Salt Lake City, Why Gallbladder Operations Fail to Relieve Symptoms.
Allan C. Barnes, Columbus, Ohio, The General Practitioner and Carcinoma of the Cervix.
Jack S. Guyton, Baltimore, Differential Diagnosis of an Inflamed Eye.
Charles H. Brown, Cleveland, Treatment of Ulcerative Colitis with Results of Surgical Therapy at the Cleveland Clinic.
Philip Thorek, Chicago, The Acute Abdomen.
O. Spurgeon English, Philadelphia, Emotional Common Denominators in Psychosomatic Disease.
Arthur C. Allen, New York, Medical Diseases of the Kidney.
George B. Logan, Rochester, Minn., Allergic Disease of the Respiratory Tract in Childhood.
William W. Scott, Baltimore, Importance of Blood in the Urine.
Edgar Hull, New Orleans, Misconceptions About the Clinical Picture of Chronic Pulmonary Conditions.
Thomas C. Galloway, Evanston, Ill., Bulbar Poliomyelitis.
Winthrop M. Phelps, Baltimore, Md., Cerebral Palsy.

On Monday at 7 p. m. the Oklahoma County Medical Society will entertain with its annual dinner in honor of Dr. John W. Cline, San Francisco, President of the American Medical Association, who will address the conference on "Problems Confronting Medicine in the Immediate Future." There will be panels and

medical and surgical luncheons each day. The registration fee is $15, which includes all luncheons, dinner, and social functions. Hotel reservations may be made with Muriel R. Waller, Executive Secretary, 512 Medical Arts Building, Oklahoma City.

PENNSYLVANIA

Society News.—At the annual dinner meeting of the Pennsylvania Psychiatric Society in Pittsburgh Sept. 20, Dr. Henry W. Brosin spoke on "Current Activities at the Western Psychiatric Institute and Clinics." The following officers were elected for the coming year: Dr. Robert H. Israel, Warren, president; Dr. Philip Q. Roche, Philadelphia, president-elect, and Dr. M. Royden C. Astley, Philadelphia, secretary-treasurer.——The first fall meeting of the Pennsylvania Academy of Physical Medicine and Rehabilitation was held on Oct. 18 at the Philadelphia County Medical Society building. The newly elected president, Dr. Herman L. Rudolph of Reading presided. Others elected for the coming year are Dr. Frank L. Follweiler, Jenkintown, vice-president; Dr. J. Murl Johnston, Pittsburgh, treasurer, and Dr. Charles A. Furey, Philadelphia, secretary. The program included a paper by Dr. Bernard D. Judovich, Philadelphia, "Reginal Therapy in Painful Syndromes." This was followed by a "Résumé of Outstanding Papers at the Denver Meeting," presented by Dr. George Morris Piersol and Dr. Emory K. Stoner, Philadelphia.

Philadelphia

Annual deSchweinitz Lecture.—The fourteenth annual deSchweinitz Lecture, sponsored by the section of ophthalmology, College of Physicians of Philadelphia, will be given Nov. 15 by Dr. Peter C. Kronfeld, Chicago, on "Tonographic Studies of Early Glaucomas."

Personal.—Dr. Robert A. Kimbrough, chairman, department of obstetrics, Graduate School of Medicine, University of Pennsylvania, has been appointed director of the division of obstetrics and gynecology of Pennsylvania Hospital, succeeding the late Dr. Clifford B. Lull. Dr. Kimbrough has been associated with Pennsylvania Hospital since 1927.

Society News.—The Philadelphia Psychiatric Society invites interested persons to attend a lecture by Prof. H. C. Rumke on "Psychological Troubles of Healthy Men," at the College of Physicians on Nov. 12 at 8 p. m. Dr. Rumke is professor of psychiatry at the University of Utrecht, and will be passing through the United States on his way to Mexico to address the World Federation of Mental Health.

Symposium on Drug Addiction.—This symposium with Dr. P. F. Lucchesi as moderator was held by the medical staff of the Philadelphia General Hospital Oct. 18. The program was as follows:

M. L. Harney, assistant to the Federal Commissioner of Narcotics, Public Health Aspects.
Havelock F. Fraser, Addiction Research Center, USPHS Hospital, Lexington, Ky., Medical Aspects of Addiction and Withdrawal.
Baldwin L. Keyes, Jefferson Medical College, Psychiatric Problems in Addiction.

Pittsburgh

Alumni Scientific Day.—The first annual scientific day of the Alumni Association of the University of Pittsburgh Medical School will be observed Nov. 9 in the Mellon Institute Auditorium from 10 a. m. to 5 p. m. The scientific program includes the following:

Jacob P. Greenhill, Chicago, Progress in Obstetrics and Gynecology.
Louis A. Brunsting, Rochester, Minn., Cortisone and Corticotropin (ACTH) as Applied to Diseases of the Skin.
Lewis Dexter, Boston, Indications for Surgery in Treatment of Mitral Stenosis.
E. Perry McCullagh, Cleveland, Advances in Clinical Endocrinology.
Harold W. Jacox, New York, Evaluation and Limitations of Radiation Therapy.

The alumni of the university are asked to contribute $5 for the presentation of this program and the luncheon. The alumni of other medical schools are also invited and are asked to pay the same assessment. Scientific exhibits have been prepared by the University of Pittsburgh Medical School and various hospitals in the city of Pittsburgh. Admission to the auditorium and exhibits is by ticket only.

SOUTH CAROLINA

Fowler Lectures on Alcoholism and Drug Addiction.—On Sept. 20 and 21 the second annual series of Fowler Lectures was held at Edgewood Sanitarium Foundation, Orangeburg. The series took the form of a two-day session on alcoholism and drug addiction with three additional lectures on the subject "Religion and Psychiatry." Included on the program of the symposium were Dr. Harris Isbell, medical director, U. S. Public Health Service Hospital, Lexington, Ky.; Leon Greenberg of Yale University, New Haven, Conn.; Francis McPeak, minister and industrial counselor, Chicago; Dr. Raymond A. McCarthy, director of educational activities on the Connecticut Commission on Alcoholism, and Aaron Rutledge, minister and professor at Furman University, Greenville, S. C. The Fowler Lectures included addresses, discussion periods, and films. Not only physicians, social workers, nurses, psychologists, and welfare workers were in attendance from North Carolina, South Carolina, and Georgia, but also educators, clergymen, legislators, judges, youth-group leaders, parent-teacher members, mental hygiene groups, police forces, and the public. Edgewood Sanitarium Foundation is an institution for the treatment of mental diseases and nervous disorders.

SOUTH DAKOTA

University Promotions.—Promotions have been awarded to four members of the staff of the University of South Dakota School of Medical Sciences, Vermillion. Dr. Theodore H. Sattler, Yankton, has been promoted from clinical associate professor to full clinical professor of medicine, and Dr. Brooks Ranney, Yankton, from clinical associate professor to clinical professor of obstetrics and gynecology. Dr. Willard V. Thompson, assistant professor, has been promoted to associate professor and chairman of the department of pathology. Willard O. Reed, Ph.D., who has been an associate in physiology, is now assistant professor of physiology. He joined the staff in 1949.

TEXAS

Cancer Research Grants.—The Damon Runyon Memorial Fund for Cancer Research, Inc., has made two grants of $5,000 each to the University of Texas Medical Branch, Galveston. One grant has been made to the Pharmacology Laboratory under the direction of George A. Emerson, Ph.D., for the study of "The Effect of Substituted Purine and Pyrimidine Analogues on the Iron, Zinc, Copper and Cobalt Content of Precancerous and Cancerous Tissues." The other grant has been made to the Tissue Culture Laboratory under the direction of Charles M. Pomerat, Ph.D., for the study of "Nuclear Cytology of Human Neoplastic Tissue Cultivated in Vitro." The funds involved were contributed in memory of the late Sam Maceo (1894-1951), a citizen of Galveston.

Award for Research on Cell Growth.—The A. L. Harris Company of Dallas, through the Southwestern Medical Foundation, has awarded a prize of $1,000 to Charles M. Pomerat, Ph.D., professor of cytology and director of the Tissue Culture Laboratory at the University of Texas Medical Branch, Galveston, for his contributions to scientific knowledge of cell growth. The award was made on the recommendation of the board of directors of the Dallas County Medical Society and by a committee representing the medical schools of Texas at a special ceremony held in Dallas on Oct. 26. Significant contributions have come from the tissue culture laboratory in cancer diagnosis, the mechanism of allergic reaction, the promotion of skin regeneration, and the discovery of pulsatile elements in cultures from human brain.

UTAH

University Postgraduate Education Program.—The University of Utah College of Medicine has established a program of postgraduate medical education with the assistance of the W. K. Kellogg Foundation. The program, which will be directed at the four so-called Intermountain states, Utah, Idaho, Arizona, and Nevada, will include short courses to be presented in Salt Lake City and elsewhere in the Intermountain area. Dr. John F. Waldo, Salt Lake City, has been designated director and is presently surveying the area before activating the actual teaching program.

VIRGINIA

Friday Evening Lecture Series.—Commemorating the 100th anniversary of the birth of Walter Reed, a graduate in 1869 of the University Department of Medicine, Charlottesville, and opening the Friday Evening Medical Lecture Series, Dr. William B. Bean, professor of internal medicine of the University of Iowa, spoke Oct. 5, on "Walter Reed, the Study of a Disciplined Mind." Remaining speakers for the fall program of the Friday Evening Medical Lecture Series are as follows:

Dr. Alan R. Moritz, Institute of Pathology, Western Reserve University, Cleveland, The Medical and Medico-Legal Implications of Unexplained Deaths, Nov. 2.
Dr. Richard J. Bing, Johns Hopkins University, Baltimore, New Aspects of the Physiology of the Human Heart, Nov. 9.
Clarence C. Little, Sc.D., Bar Harbor, Maine, Genetics in Relation to Basic and Clinical Research in Cancer, Nov. 30.
Dr. Alton Ochsner, New Orleans, Early Diagnosis and Treatment of Gastric Carcinoma, Dec. 7.

WEST VIRGINIA

Public Health Appointment.—Mr. Leon Stanley, who has lately been connected with the Alabama division of mental health, has been appointed senior psychiatric social worker for the bureau of mental hygiene, state department of health. He replaces Mr. Edgar Perretz, who has resigned to accept an appointment as director of the psychiatric social service of the Columbus Receiving Hospital, Ohio State University Medical Center.

WISCONSIN

Dr. Moritz to Speak in Madison.—The Medical School Society of the University of Wisconsin, Madison, will present on Oct. 30 a lecture entitled "The Law and Medicine," by Dr. Alan R. Moritz. Dr. Moritz is professor of pathology at the Western Reserve University School of Medicine in Cleveland and an authority on the subject of forensic medicine. The lecture will be held in the Auditorium, Service Memorial Institute at 8 p. m.

Public Health Appointment.—Dr. Milton Feig, former district health officer of the Green Bay area, has been named successor to Dr. Arthur R. Zintek, Madison, director of the section on preventable diseases of the state board of health. Dr. Zintek resigned Sept. 1 to accept a position with the Northwestern Mutual Life Insurance Company in Milwaukee. Dr. Feig joined the state board of health in 1949. He is a specialist certified by the American Board of Preventive Medicine and Public Health.

University Appoints VA Physicians to University Staff.—Five members of the new Madison Veterans Administration Hospital staff have been appointed as members of the University of Wisconsin Medical School staff without salary or tenure. They are Dr. William P. Young, associate professor of surgery; Dr. Bruce J. Longley, assistant professor of surgery; Dr. John K. Curtis, associate professor of medicine; Dr. Frank C. Larson, assistant professor of medicine, and Dr. Chalmer Davee, assistant professor of clinical medicine.

Student Loan Fund.—A quarter million dollar loan fund will be raised by the State Medical Society of Wisconsin to help needy students through medical school and locate in the state. Preference will be given to students who enroll at the University of Wisconsin or at Marquette University Medical School. The money will be raised by contributions from physicians and the public, and loans will be made as soon as $20,000 is obtained. The fund is the realization of a proposal made by Dr. Henry H. Christofferson, Colby, then president of the medical society, at the 1950 annual meeting, who will serve as chairman of the board of trustees of the fund. Other members of the board are Dr. Albion H. Heidner, West Bend, president-elect, vice-chairman; Charles H. Crownhart, Madison, secretary of the society, secretary-treasurer; The Hon. Oscar A. Rennebohm, Madison, former governor of Wisconsin; The Hon. A. Matt Werner, editor of the *Sheboygan Press* and a regent of the University of Wisconsin; Dr. Ira R. Sisk, Madison, former treasurer of the state society; and Dr. Raymond G. Arveson, Frederic, chairman of the council. Contributions or inquiries concerning the fund may be directed to the State Medical Society of Wisconsin at 704 East Gorham St., Madison.

GENERAL

Industrial Medical Meeting.—The joint scientific meeting of the Central States and the Chicago Societies of Industrial Medicine and Surgery will be held from 2 to 5 p. m. Oct. 28 at the La Salle Hotel, Chicago. The program is as follows:

George V. LeRoy, Hines, Ill., Industrial Application of Radioactivity.
H. Close Hesseltine, Chicago, The Menopause in the Employee.
Wesley A. Gustafson, Chicago, Recent Advances and Treatment of Head Injuries.
Wayne B. Slaughter, Chicago, Treatment of Maxillofacial Injuries.

Clinical and Climatological Association Meeting.—The annual meeting of the American Clinical and Climatological Association will be held at Skytop Lodge in Skytop, Pa., Nov. 5-7, under the presidency of Dr. John Minor, Washington, D. C. Among the 24 papers to be read before the association is the Gordon Wilson Lecture. Dr. Andre Cournand, professor of medicine at Columbia University College of Physicians and Surgeons, New York, will speak on "Certain Types of Pulmonary Granulomata and Fibroses."

Society News.—The New England Obstetrical and Gynecological Society will hold its annual meeting Oct. 31 at the Hotel Somerset in Boston under the presidency of Dr. Arthur T. Hertig, Boston. During the morning, clinics will be held at Boston City Hospital, Carney Hospital, and the Free Hospital for Women, Brookline, Mass., and dry clinics will be held at the Hotel Somerset. Visiting speakers in the afternoon program include Dr. George W. Waterman, Providence, R. I., speaking on "Carcinoma of the Endometrium," and Dr. John L. McKelvey, Minneapolis, speaking on "Carcinoma of the Vulva."

Medico-Labor Panel.—On Oct. 16 the Monroe County Medical Society presented a panel discussion on "What Labor Thinks of Medicine." The moderator was The Honorable Daniel J. O'Mara, Monroe County judge. Discussants were Mr. Lawrence J. Bradley, administrator, Genesee Hospital; Mr. Fred J. Brown, secretary, Central Trades and Labor Council, A. F. of L.; Mr. Julius Hoesterey Jr., Lithographer's Union delegate, Executive Board, C. I. O. Council; Dr. Donovan M. Jenkins, vice-president, Monroe County Medical Society; Dr. Charles S. Lakeman, public relations chairman, Monroe County Medical Society; Mr. Sherman D. Meech, managing director, Rochester Hospital Service Corporation, and Mr. Charles M. Royle, executive director, Rochester Regional Hospital Council.

Magazine on Air Pollution.—*Air Repair*, a magazine devoted to the problems of air purification, began publication in July as the official organ of the Air Pollution and Smoke Prevention Association of America, which moved its headquarters from Chicago to the Mellon Institute in Pittsburgh last winter. Four issues per year are contemplated. The magazine is to be a medium of exchange and information and will report the latest activities and improvements in methods, techniques, and equipment. The Air Pollution and Smoke Prevention Association of America has more than 700 members at present. The magazine *Smoke* ceased publication a few years ago when the scope of the organization was broadened to include interest in all phases of air contamination. Its successor is the new journal *Air Repair*.

Model Community Survey.—A survey, designed for the use of communities in studying their chronic illness problems and taking inventory of existing facilities and services, has been issued by the Commission on Chronic Illness. It was prepared under the direction of Dr. Morton L. Levin during the period he served as director of the commission. This publication includes a detailed outline of subjects that should be covered in making a comprehensive survey of facilities and services available for the prevention and early detection of chronic disease and the care and rehabilitation of the chronically ill and a set of schedules for obtaining information about prevalence of illness and existing community facilities and services. Copies of the present edition of the survey plan may be obtained from the Commission on Chronic Illness, 535 N. Dearborn St., Chicago 10, for $1.

Research on Multiple Sclerosis.—A Panel of International Neurologists has recently been established with headquarters at the National Multiple Sclerosis Society, 270 Park Ave., New York 17. Dr. Cornelius H. Traeger, medical director of the

society, is founder of the panel which comprises 56 neurologists from 26 countries. Many of these physicians have been engaged in research work on multiple sclerosis and related neurological disorders. Reports of all research will be sent to Dr. Traeger, who in turn will be in a position to keep the corresponding neurologists informed of all developments in this country. The National Multiple Sclerosis Society has established a liaison with the National Research Council, Division of Medical Sciences, Medical Sciences Information Exchange, Washington, D. C. The major purpose of the National Multiple Sclerosis Society is to support and stimulate research in multiple sclerosis and related nerve disorders. Since its formation about five years ago it has supported, through grants, 18 research projects at a total cost of $344,339.

Federation Changes Name and Purpose.—The National Federation of Obstetric-Gynecologic Societies on June 13 reconstituted itself as a scientific society to be called the American Academy of Obstetrics and Gynecology. The following officers were elected: Drs. Woodard D. Beacham, New Orleans, president; Carl P. Huber, Indianapolis, president-elect; Louis H. Douglass, Baltimore, vice-president; Herbert E. Schmitz, Chicago, treasurer, and Ralph A. Reis, Chicago, secretary. The academy was incorporated on Aug. 4 as a nonprofit corporation under the laws of the state of Illinois. Its objects are listed in the constitution and bylaws adopted at a meeting held at Hot Springs, Va., on Sept. 5. They include "fostering and stimulating interest in obstetrics and gynecology and all aspects of the work for the welfare of women which properly come within the scope of obstetrics and gynecology." The first annual clinical meeting will be held in Chicago during the winter of 1952-53. Applications for fellowship may be obtained from the Secretary's Office, 116 South Michigan Ave., Chicago 3.

Anesthesiologists to Meet.—The American Society of Anesthesiologists will hold its annual meeting at the Hotel Statler, Washington, D. C., Nov. 5-8 under the presidency of Dr. Urban H. Eversole, Boston. Among the papers to be presented will be a symposium on shock, Thursday at 2 p. m., Dr. Donald H. Stubbs, Washington, D. C., serving as chairman. The panel will be made up of the following:

Perry P. Volpitto, Augusta, Ga., Evaluation of Susceptibility to Shock: The Starting Point—Reserve.
Charles R. Stephen, Durham, N. C., The Relation of Light or Deep Anesthesia to Shock.
John Adriani, New Orleans, The Use of Drugs in Shock.
J. Ross Veal, Washington, D. C., Intra-Arterial Transfusion in Shock Due to Hemorrhage.
Emanuel M. Papper, New York, The Relation of Heart Failure to Shock: Cardiac Arrest.

Beginning Monday, 120 refresher courses have been provided. At a banquet at 6 p. m. on Wednesday Dr. Frank H. Lahey, Boston, will be presented with a special tribute by the society as an expression of appreciation for his support and efforts to advance anesthesiology.

WHO Fellowships for Study Abroad.—The World Health Organization is offering 10 to 14 fellowships to the United States for foreign study during 1952 in the field of health. The Fellowship Selection Board, established by Surgeon General Leonard Scheele, consists of Dr. Joseph W. Mountin, U. S. Public Health Service; Dr. Leona Baumgartner, New York, American Public Health Association; and Dr. Walter A. Bloedorn, Washington, D. C., Association of American Medical Colleges. Applications will be considered in various branches of public health or such allied fields as medical or nursing education. Applicants must be engaged in full-time public health or educational work. Knowledge of the language of the country to be visited is necessary. Nonfederal workers will be given preference. To date, grants have not been given for research activities alone. All grants given in the past have been for two or three month periods. The World Health Organization provides transportation to and in the country visited, with a stipend from $160 to $300 a month. Application blanks may be obtained from the Division of International Health, U. S. Public Health Service, Washington, D. C., and must be filed in triplicate by Jan. 1, 1952.

National Conference on Civil Defense.—The National Civil Defense Conference, the first of its kind, is to be held at the Palmer House, Nov. 9-10, under the joint sponsorship of the American Medical Association, the American Hospital Association, and the Association of State and Territorial Health Officers. State public health officers, hospital administrators, and representatives of state medical societies will meet with the government civil defense authorities. The keynote address will be given by Dr. James C. Sargent, Milwaukee, chairman of the Council on National Emergency Medical Service of the American Medical Association. Other speakers at the opening session include the following:

Herman E. Hilleboe, Albany, Public Health Aspects of Civil Defense.
Mr. Anthony Eckert, Perth Amboy, N. J., Hospital Civil Defense Planning.
Justin J. Stein, Los Angeles, Role of State Medical Society in Civil Defense.

A panel with speakers from the Federal Civil Defense Administration will be held in the afternoon under the chairmanship of Dr. William L. Wilson, Washington, D. C., assistant administrator. On Saturday morning following an address by Millard Caldwell, administrator, Federal Civil Defense Administration, four discussion groups will take up Professional Training, Mobile Support, Recruitment and Organization, and Organizing and Equipping an Improvised Civil Defense Hospital System.

National Academy of Sciences Meeting.—This academy will hold its public autumn meeting for the presentation of scientific papers Nov. 5-7, at morning sessions in the Sterling Law Building at Yale University, New Haven, Conn. Among the papers to be presented are the following:

G. Evelyn Hutchinson, New Haven, Conn., Possible Role of Sexual Selection in the Etiology of Endemic Goitre.
Werner Bergmann, New Haven, Conn., Haliclonasterol and Palysterol: Two Natural Sterols.
John R. Paul, New Haven, Conn., Antibodies and Geography.
Carl J. Wiggers, Cleveland, Effect of Limited and Distributed Distensibility on the Pressure Pulses in the Arterial System.
Neal E. Miller, New Haven, Conn., Behavioral Effects of Food via Stomach Fistula Compared with Those of Food via Mouth.
Donald J. Fluke, New Haven, Conn., Ruth M. Drew, Upton, L. I., N. Y., and Ernest Pollard, New Haven, Conn., The Effect of Ionizing Radiation on the Transforming Factor of Pneumococci.
Joseph L. Melnic, New Haven, Conn., Electron Microscope Studies of Viruses and Cells.
Herbert M. Evans, Marjorie M. Nelson, and C. Willett Asling, Berkeley, Calif., Multiple Congenital Abnormalities Resulting from Acute Folic Acid Deficiency During Gestation.
Paul R. Burkholder, New Haven, Conn., Microbiological Studies on the Intrinsic Factor of Castle.
Charles B. Huggins and Dalbert M. Bergenstal, Chicago, Influence of Bilateral Adrenalectomy, Adrenocorticotrophin, and Cortisone Acetate on Certain Human Tumors.
William S. Tillett, New York, Biological Effects of the Streptococcal Enzymes, Streptokinase and Streptodornase, on Local Areas of Disease in Patients.
Donald H. Barron, New Haven, Conn., Palcental Morphology and Fetal Respiration.
Edwin J. Cohn, James L. Tullis, Douglas M. Surgenor, William H. Batchelor, and Maurice D'Hont, Cambridge, Mass., Biochemistry and Miomechanics of Blood Collection, Processing, and Analyzing.

The National Academy of Sciences is an association of individual scientists and scientific societies founded in 1863 under a Congressional Charter to further science and promote the national welfare by advising the government on scientific matters. Its 10 sections include zoology, anatomy, physiology, pathology, anthropology, and psychology. The National Research Council was established within the academy in 1916.

Surgeons Clinical Congress.—The clinical congress of the American College of Surgeons will be held Nov. 5-9 in San Francisco with headquarters at the Civic Auditorium. Dr. Henry W. Cave, New York, president, will preside at the general assembly, when the subject of Collaboration in Hospital Standardization will be discussed by Dr. Arthur W. Allen, chairman of the board of regents of the college, Dr. Frank R. Bradley, St. Louis, trustee of the American Hospital Association, Dr. Dwight H. Murray, Napa, Calif., Chairman of the Board of Trustees, American Medical Association, and Dr. Dwight L. Wilbur, San Francisco, representing the American College of Physicians. At the meeting on the first evening Dr. Alton Ochsner, New Orleans, will be installed as president, and Dr. Paul B. Magnuson, Chicago, professor emeritus at Northwestern University Medical School, will deliver the Martin Memorial Lecture on "Remove Not the Ancient Landmark." At the convocation on Friday evening, some 900 initiates will be received into fellowship and several honorary fellowships will be conferred. The Fellowship Address

will be given by Dr. J. Roscoe Miller, Evanston, Ill., president of Northwestern University. Other evening sessions will be as follows: Tuesday, Medical Defense Program with Col. William L. Wilson of Washington participating; Wednesday, the Fracture Oration, delivered by Sir Reginald Watson-Jones of London, and a symposium on "Metabolic Disturbances During Surgical Care," and Thursday, discussion of radiation therapy, applications of radioactive isotopes, and the status of antibiotics. In addition, on the same evenings there will be separate sessions for ophthalmologists and for otorhinolaryngologists. Twenty-six hospitals in San Francisco and East Bay communities and the medical schools of the University of California and Stanford University are planning clinics, demonstrations, and other events. Letterman Army Hospital surgeons are arranging operative clinics which will be telecast, in color, to the Civic Auditorium. Forums on fundamental surgical problems and some of the other sessions will be held in the Fairmont and Mark Hopkins hotels.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States in the weeks ended as indicated:

Area	Oct. 13, 1951	Oct. 6, 1951	Oct. 14, 1950
New England States			
Maine	1	4	4
New Hampshire	..	1	..
Vermont	..	..	2
Massachusetts	3	14	21
Rhode Island	1	2	1
Connecticut	9	23	32
Middle Atlantic States			
New York	54	72	205
New Jersey	16	20	44
Pennsylvania	34	49	77
East North Central States			
Ohio	66	69	125
Indiana	12	17	54
Illinois	65	87	100
Michigan	75	98	114
Wisconsin	64	102	65
West North Central States			
Minnesota	30	34	28
Iowa	8	17	57
Missouri	16	51	28
North Dakota	4	6	2
South Dakota	3	8	3
Nebraska	17	21	22
Kansas	24	39	23
South Atlantic States			
Delaware	..	..	2
Maryland	5	5	60
District of Columbia	1	3	10
Virginia	14	13	51
West Virginia	12	16	12
North Carolina	7	11	28
South Carolina	2	3	8
Georgia	10	16	23
Florida	6	4	20
East South Central States			
Kentucky	10	17	40
Tennessee	28	31	25
Alabama	14	16	9
Mississippi	42	29	18
West South Central States			
Arkansas	16	9	6
Louisiana	14	27	9
Oklahoma	29	16	9
Texas	56	55	70
Mountain States			
Montana	5	7	2
Idaho	13	1	18
Wyoming	15	13	2
Colorado	30	44	15
New Mexico	5	5	7
Arizona	11	8	13
Utah	16	34	4
Nevada	1	2	..
Pacific States			
Washington	10	18	24
Oregon	17	20	29
California	125	145	66
United States	1,016	1,278	1,606
Territories and Possessions			
Alaska	..	4	9
Hawaii	..	2	1

LATIN AMERICA

Anniversary of University of Mexico.—Under the auspices of the National Independent University of Mexico, a scientific congress was held in Mexico City, Sept. 24-30, in connection with the 400th anniversary of the founding of the university. The congress included five sections at which more than 1,500 papers and reports were presented. The Division of Biological Sciences and Medicine was under the direction of Dr. Ignacio Gonzales Guzman, and included sections on the biological sciences and the medical specialties. Meetings were held at the Cardiology Institute, the Children's Hospital, the Hospital for Diseases of Nutrition, the General Hospital, and the Institute for Tropical Diseases. Over 600 reports in the medical sciences were presented. Honor guests, invited from the various countries of the world, participated in the discussions. From the United States guests contributing to the medical program included Dr. Karl F. Meyer, director of the Hooper Foundation for Medical Research, University of California, San Francisco; Dr. Henry Helmholtz, professor of pediatrics of the Mayo Clinic, Rochester, Minn.; Dr. Eleazar S. Guzman Barron, professor of biochemistry of the University of Chicago; Dr. Lewis N. Katz, director of cardiovascular research of the Michael Reese Hospital, Chicago; and Chauncey D. Leake, Ph. D., vice-president of the University of Texas Medical Branch, Galveston.

FOREIGN

International Anti-Tuberculosis Center.—Thailand's first international anti-tuberculosis center will soon be opened in Bangkok, under the auspices of the World Health Organization, as one of several such institutions designed to serve as demonstration training centers for all aspects of tuberculosis control. It will be equipped with an x-ray examination laboratory and modern facilities for tuberculin testing and BCG vaccination. The activities will also include nursing services and home visiting. Young doctors and nurses from several countries in southeast Asia are expected to be granted WHO fellowships for training at the center. WHO teaching personnel in the center includes Dr. Marcel Mistal (Switzerland), a tuberculosis specialist; a Mr. Williams (United Kingdom), an x-ray technician; Dr. C. V. Y. Tardon (Chile), an epidemiologist, and Miss C. Eriksen (Canada), a public health nurse.

DEATHS IN FOREIGN COUNTRIES

Dr. Emile Brumpt, authority on parasitology and tropical medicine, died on July 7 in Paris, aged 74. Just prior to his death, he had been informed that he was to receive the Theobald Smith Medal at the forthcoming meeting of the American Society and American Academy of Tropical Medicine.

EXAMINATIONS AND LICENSURE

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 24-26, 1952. Sec., Dr. D. G. Gill, 537 Dexter Ave., Montgomery 4.

ARIZONA:* *Examination.* Phoenix, Oct. 16-18. *Reciprocity.* Phoenix, Oct. 20. Sec., Dr. J. H. Patterson, 316 W. McDowell Road, Phoenix.

ARKANSAS:* *Regular.* Little Rock, Nov. 8-9. Sec., Dr. Joe Verser, Harrisburg. *Homeopathic.* Little Rock, Oct. 18-19. Sec., Dr. Carl Sperry Bungart, Fort Smith. *Eclectic.* Sec., Dr. Frank C. Smith, 2301 Broadway, Little Rock.

CALIFORNIA: *Written.* Sacramento, Oct. 15-18. *Oral.* San Francisco, Nov. 10. Sec., Dr. Frederick N. Scatena, 1020 N St., Sacramento.

CONNECTICUT:* *Regular.* Hartford, Nov. 13-14. Sec. to Bd., Dr. Creighton Barker, 160 St. Ronan St., New Haven. *Homeopathic.* Derby, Nov. 6-17. Sec., Dr. Donald A. Davis, 38 Elizabeth St., Derby.

DELAWARE: *Examination.* Dover, Jan. 8-10. *Endorsement.* Dover, Jan. 17. Sec., Dr. J. S. McDaniel, 229 South State St., Dover.

DISTRICT OF COLUMBIA:* *Examination.* Washington, Nov. 13-14. Sec., Dr. Daniel L. Seckinger, 4130 E. Municipal Bldg., Washington.

FLORIDA:* *Examination.* Jacksonville, Nov. 25-27. Sec., Dr. Homer L. Pearson, 701 DuPont Bldg., Miami.

GUAM: The Commission on Licensure will meet whenever a candidate appears or submits his credentials. Ex. Sec., Dr. John K. Battenfield, Agana.

HAWAII: *Examination.* Honolulu, Jan. 14-17. Final date for filing application is Dec. 14. Sec., I. L. Tilden, 1020 Kapiolani St., Honolulu.

IDAHO: Boise, Jan. 7-9. Sec., Mr. Armand L. Bird, 305 Sun Bldg., Boise.

INDIANA: Indianapolis, June 1952. Sec., Dr. Paul R. Tindall, 1138 K of P Bldg., Indianapolis 4.

IOWA:* *Examination.* Des Moines, Dec. 3-5. Sec., Dr. M. A. Royal, 506 Fleming Bldg., Des Moines.

KANSAS: Topeka, Dec. 12-13. Sec., Dr. O. W. Davidson, 772 New Brotherhood Bldg., Kansas City.

KENTUCKY: *Examination.* Louisville, Dec. 11-13. Sec., Dr. Bruce Underwood, 620 S. 3rd St., Louisville.

MAINE: Portland, Nov. 13-14. Sec., Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Examination.* Baltimore, Dec. 11-14. Sec., Dr. Lewis P. Gundry, 1215 Cathedral St., Baltimore.

MASSACHUSETTS: *Examination.* Boston, Jan. 15-18. Sec., Dr. Robert C. Cochrane, Room 37 State House, Boston.

MINNESOTA: * Minneapolis, Oct. 16-18. Sec., Dr. Julian F. DuBois, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: *Reciprocity.* Jackson, December. *Examination.* Jackson, June. Asst. Sec., Dr. R. N. Whitfield, Old Capitol Bldg., Jackson.

MISSOURI: *Examination.* Kansas City, Oct. 18-20. *Reciprocity.* Oct. 17. Exec. Sec., Mr. John A. Hailey, State Capitol Bldg., Jefferson City.

NEW JERSEY: *Examination.* Trenton, Oct. 16-19. Sec., Dr. E. S. Hallinger, 28 W. State St., Trenton.

NEW YORK: *Examination.* Albany, Buffalo, New York and Syracuse, Oct. 31-Nov. 3. Sec., Dr. Jacob L. Lochner, Jr., 23 S. Pearl St., Albany.

NORTH DAKOTA: Grand Forks, Jan. 2-5. Sec., Dr. C. J. Glaspel, Grafton.

OKLAHOMA:* *Examination.* Oklahoma City, June 4-5. Sec., Dr. Clinton Gallaher, 813 Braniff Bldg., Oklahoma City.

PENNSYLVANIA: Philadelphia, January. Acting Sec., Mrs. M. G. Steiner, 351 Education Bldg., Harrisburg.

PUERTO RICO: *Examination.* San Juan, March 4. Sec., Mr. Luis Cueto Coll, Box 3717, Santurce.

SOUTH CAROLINA: *Examination.* Columbia, Nov. 12-14. Sec., Dr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA:* *Examination.* Sioux Falls, Jan. 15-16. Ex. Sec., Mr. John C. Foster, 300 First National Bank Bldg., Sioux Falls.

TEXAS:* *Examination.* Houston, Dec. 3-5. Sec., Dr. M. H. Crabb, 1714 Medical Arts Bldg., Fort Worth.

VIRGINIA *Examination.* Richmond, Dec. 6-8. Final date for filing application is Nov. 24. Sec., Dr. K. D. Graves, 631 First St., S.W., Roanoke.

VIRGIN ISLANDS: Charlotte Amalie, Nov. 7-8 Sec., Dr. Earle M. Rice, St. Thomas.

WISCONSIN:* Madison, Jan. 8-10. Sec., Dr. A. C. Koehler, River Falls.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: *Examination.* On application. Juneau or other towns in Territory as decided by Board. *Reciprocity.* On application. Sec., Dr. C. Earl Albrecht, Box 1931, Juneau.

COLORADO: *Examination.* Denver, Dec. 5-6. Sec., Dr. Esther B. Starks, 1459 Ogden St., Denver.

DISTRICT OF COLUMBIA: *Examination.* Washington, Oct. 22-23. Sec., Dr. Daniel L. Seckinger, 4130 E. Municipal Bldg., Washington.

FLORIDA: Gainesville, Nov. 10. Sec., Mr. M. W. Emmel, Box 340, University of Florida, Gainesville.

NEW MEXICO: *Examination.* Santa Fe, Dec. 16. Sec., Mrs. Marguerite Cantrell, Box 1592, Santa Fe.

OKLAHOMA: *Examination.* Oklahoma, April 14. Sec., Dr. Clinton Gallaher, 813 Braniff Bldg., Oklahoma City.

OREGON: *Examination.* Portland, Dec. 1. Sec., Dr. Charles D. Byrne, State Board of Higher Education, University of Oregon, Eugene.

RHODE ISLAND: *Examination.* Providence, Nov. 14. Sec., Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH DAKOTA: *Examination.* Vermillion, Dec. 7-8. Sec., Dr. Gregg M. Evans, 310 E. 15th St., Yankton.

TENNESSEE: *Examination.* Memphis, Dec. 27-28. Sec., Dr. O. W. Hyman, 864 Union Ave., Memphis.

TEXAS: *Examination.* Austin, Oct. 19-20. Chief Clerk, Mr. B. H. Kirk, 306 Nalle Bldg., Austin.

WISCONSIN: *Examination.* Milwaukee, Dec. 1. Madison, April 5. Sec., Mr. W. H. Barber, Ripon College, Ripon.

* Basic Science Certificate required.

MEETINGS

AMERICAN MEDICAL ASSOCIATION CLINICAL SESSION, Los Angeles, Dec. 4-7. Dr. George F. Lull, 535 N. Dearborn St., Chicago 10, Secretary.

AMERICAN CLINICAL AND CLIMATOLOGICAL ASSOCIATION, Skytop, Pa., Nov. 5-7. Dr. Marshall N. Fulton, 124 Waterman St., Providence, R. I., Secretary.

AMERICAN COLLEGE OF SURGEONS, Fairmont Hotel, San Francisco, Nov. 5-9. Dr. Michael L. Mason, 40 E. Erie St., Chicago 11, Secretary.

AMERICAN PUBLIC HEALTH ASSOCIATION, Civic Auditorium, San Francisco, Oct. 29-Nov. 2. Dr. Reginald M. Atwater, 1790 Broadway, New York 19, Executive Secretary.

AMERCAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS, Chicago, Nov. 4-5. Dr. O. J. Pollak, Quincy City Hospital, Quincy 69, Mass., Secretary.

AMERICAN SOCIETY OF ANESTHESIOLOGISTS, Washington, D. C., Nov. 5-8. Dr. J. Earl Remlinger Jr., 188 W. Randolph St., Room 909, Chicago 1, Secretary.

AMERICAN SOCIETY OF TROPICAL MEDICINE, Congress Hotel, Chicago, Nov. 15-17. Dr. Quentin M. Geiman, 25 Shattuck St., Boston 15, Secretary.

ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASES, Hotel Roosevelt, New York, Dec. 14-15. Dr. Clarence C. Hare, 170 Maple Ave., White Plains, N. Y., Secretary.

ASSOCIATION OF AMERICAN MEDICAL COLLEGES, French Lick Springs Hotel, French Lick, Ind., Oct. 29-31. Dr. Dean F. Smiley, 185 N. Wabash Ave., Chicago 1, Secretary.

ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICERS, Washington, D. C., Nov. 26-30. Dr. John D. Porterfield, 306 Ohio Depts. Bldg., Columbus 15, Ohio, Secretary.

CENTRAL SOCIETY FOR CLINICAL RESEARCH, Drake Hotel, Chicago, Nov. 2-3. Dr. Kenneth G. Kohlstaedt, 960 Locke St., Indianapolis 7, Secretary.

INDIANA STATE MEDICAL ASSOCIATION, Indianapolis, Oct. 29-31. Miss Lucille Kribs, 23 E. Ohio St., Indianapolis 4, Acting Secretary.

NATIONAL ASSOCIATION OF CLINIC MANAGERS, Buena Vista Hotel, Biloxi, Miss., Oct. 29-31. Mr. Floyd R. Detert, Marshfield Clinic, Marshfield, Wis., Secretary.

NATIONAL CONFERENCE ON PHYSICIANS AND SCHOOLS, Moraine Hotel, Highland Park, Ill., Nov. 6-8. Dr. W. W. Bauer, 535 North Dearborn St., Chicago 10, Secretary.

NORTH CENTRAL MEDICAL CONFERENCE, Hotel Radisson, Minneapolis, Nov. 11. Mr. R. R. Rosell, 496 Lowry Medical Arts Bldg., St. Paul 2, Secretary.

NORTH PACIFIC SURGICAL ASSOCIATION, Vancouver, B. C., Canada, Nov. 16-17. Dr. J. A. Duncan, 509 Olive Way, Seattle, Wash., Secretary.

OKLAHOMA CITY CLINICAL SOCIETY, Biltmore Hotel, Oklahoma City, Oct. 29-Nov. 1. Mrs. Muriel R. Waller, 612 Medical Arts Bldg., Oklahoma City, Executive Secretary.

OMAHA MID-WEST CLINICAL SOCIETY, Hotel Paxton, Omaha, Oct. 29-Nov. 2 Dr. L. E Moon, 1031 Medical Arts Bldg., Omaha 2, Secretary.

PUERTO RICO MEDICAL ASSOCIATION, Santurce, Dec. 12-16. Dr. Victor J. Montilla, P. O. Box 3866, Santurce, Secretary.

RADIOLOGICAL SOCIETY OF NORTH AMERICA, Chicago, Dec. 3-7. Dr. Donald S. Childs, 713 E. Genesee St., Syracuse 2, N. Y., Secretary.

STATE MEDICAL JOURNAL CONFERENCE, Chicago, Nov. 12-13. Mr. A. J. Jackson, 535 North Dearborn St., Chicago 10, Secretary.

SOUTHERN MEDICAL ASSOCIATION, Dallas, Texas, Nov. 5-8. Mr. C. P. Loranz, 1020 Empire Bldg., Birmingham 3, Ala., Secretary.

SOUTHERN SURGICAL ASSOCIATION, The Homestead, Hot Springs, Va., Dec. 4-6. Dr. John C. Burch, 2112 West End Ave., Nashville 5, Tenn. Secretary.

WESTERN SURGICAL ASSOCATION, Broadmoor Hotel, Colorado Springs, Colo., Nov. 29-Dec. 1. Dr. Michael L. Mason, 154 E. Erie St., Chicago 11, Secretary.

INTERNATIONAL

AUSTRALASIAN MEDICAL CONGRESS, Melbourne Victoria, Australia, Aug. 22-30. Dr. C. H. Dickson, Medical Society Hall, 426 Albert St., East Melbourne, Victoria, Australia, Hon. General Secretary.

COMMONWEALTH AND EMPIRE HEALTH AND TUBERCULOSIS CONFERENCE, Central Hall, London, England, July 8-13. Dr. J. H. Harley Williams, Tavistock House North, Tavistock Sq., London, W.C.1, England, Secretary General.

INTERNATIONAL CONGRESS ON MENTAL HEALTH, Mexico City, Mexico, Dec. 11-19. Mrs. Grace E. O'Neill, Division of World Affairs, National Association on Mental Health, 1790 Broadway, New York 19, N. Y.

INTERNATIONAL CONGRESS ON NEUROPATHOLOGY, Rome, Italy, Sept. 8-13. Dr. Armando Ferraro, 722 W. 168th St., New York, N. Y., U. S. A., Secretary General.

INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, London, England, July 14-19. Dr. A. C. Boyle, 45, Lincoln's Inn Fields, London, W.C.2, England, Hon. Secretary.

PAN AMERICAN CONGRESS OF OPHTHALMOLOGY, Mexico City, Mexico, Jan. 6-12. Dr. Luis Sanchez Bulnes, Gomez Farias 19, Mexico 4, D.F., Secretary-General.

PAN AMERICAN CONGRESS OF PEDIATRICS, Montevideo, Uruguay, Dec. 5-8. Dr. Maria Luisa Saldien de Rodriguez, Avenida 18 de Julio, 1246, Montevideo, Uruguay, General Secretary.

PAN PACIFIC SURGICAL ASSOCIATION CONGRESS, Honolulu, Hawaii, Nov. 7-19. Dr. Forrest J. Pinkerton, Suite 7, Young Bldg., Honolulu, Hawaii, President.

DEATHS

Christian, Henry Asbury ✠ Brookline, Mass., since 1939 Hersey professor of theory and practice of physic, emeritus, at Harvard Medical School in Boston, died in Morrison Hospital, Whitefield, N. H., Aug. 24, aged 75, of coronary thrombosis. Dr. Christian was born in Lynchburg, Va., Feb. 17, 1876. After graduating from Johns Hopkins University School of Medicine in Baltimore in 1900, he was appointed assistant pathologist at the Boston City Hospital and from 1903 to 1907 was assistant pathologist at Children's Hospital. He was an instructor in pathology from 1903 to 1905 at Harvard Medical School, an instructor in theory and practice of physic from 1905 to 1907, assistant professor, 1907-1908, dean of the faculty of medicine from 1908 to 1912, and Hersey professor of theory and practice of physic from 1908 to 1939, when he became an emeritus professor. During World War II he was recalled to active teaching. In 1943 he served as professor of clinical medicine at Tufts College Medical School in Boston. He was physician-in-chief to the Carney Hospital from 1907 to 1912 and to the Peter Bent Brigham hospital from 1910 to 1939, when he became emeritus. In February 1936 at a regular clinical pathological conference at the Brigham Hospital, Dr. Christian was presented with a volume of medical papers dedicated to him by his former students, colleagues, and house officers as a token of affection on his 60th birthday; in 1938 his portrait was presented to the hospital corporation by some 350 friends and pupils. He was an assistant visiting physician to the Long Island Hospital in 1905 and visiting physician to the Beth Israel Hospital in Boston from 1942 to 1946. During World War I he was commissioned but was not called to active duty and continued as a major in the medical reserve corps of the Army from 1918 to 1921. In 1919 he was made resident chairman of the division of medical sciences of the National Research Council and served for one year. At the Centennial Session of the American Medical Association in June 1947, Dr. Christian received the citation and the Distinguished Service Medal. He served the Association as secretary of the Section on Pathology and Physiology from 1903 to 1905, as chairman of the section from 1905 to 1907, and as a delegate from that section in 1909. In 1916-1917 he was secretary of the Section on Practice of Medicine and a delegate from this section in 1926-1927. He was president of the American Society for Clinical Investigation in 1919, of the Interstate Postgraduate Medical Association of North America in 1931, and of the Association of American Physicians in 1935. He was a fellow of the American Academy of Arts and Sciences and the American College of Physicians, an honorary fellow of the Royal College of Physicians and Surgeons of Canada, a member of the American Association of Pathologists and Bacteriologists, American Society for Experimental Pathology, American Association for the Advancement of Science, the American Association of University Professors, and the Boston Medical Library Association. He was a corresponding member of several foreign societies, and his fraternities included the Sigma Chi, Phi Beta Kappa, Alpha Omega Alpha, and Sigma Xi. He was a specialist certified by the American Board of Internal Medicine. In 1936 he delivered the third Frank Billings Lecture of the Thomas Lewis Gilmer Foundation of the Institute of Medicine of Chicago, in 1937 the William Potter Memorial Lecture at Jefferson Medical College in Philadelphia, and in 1938 the lecture of the Sir William Osler Society of the Tufts College Medical Society. He had honorary degrees from Jefferson Medical College, Philadelphia; Randolph-Macon College, Ashland, Va.; University of Michigan, Ann Arbor; Western Reserve University, Cleveland, and the University of Western Ontario in London, Ont., Canada. He was the author of "Diagnosis and Treatment of Diseases of the Heart" and the revised "Osler's Principles and Practice of Medicine." Dr. Christian was the editor for the Oxford University Press of "The Oxford Medicine" and "Oxford Monographs on Diagnosis and Treatment" and had contributed extensively to medical literature.

✠ Indicates Fellow of the American Medical Association.

Dempster, James Herbert ✠ Detroit; born in Aylmer, Ont., Canada, May 12, 1873; Detroit College of Medicine, 1909; emeritus professor of radiology at his alma mater, now known as the Wayne University College of Medicine; an Associate Fellow of the American Medical Association; member of the American College of Radiology; had been secretary and vice-president and in 1926-1927 president of the Wayne County Medical Society; specialist certified by the American Board of Radiology; for a time head of the x-ray department of St. Mary's Hospital; at one time served in Ottawa as press correspondent in the Canadian House of Commons; formerly assistant editor of the *London Daily Advertiser* and editor of the *Windsor Record;* editor of the *Michigan State Medical Journal* from 1926 to 1939; on June 12, 1935, received an honorary degree of master of arts in literature and medicine from the Detroit Institute of Technology; author of "Medical Writing," "Pathfinders of Physiology," and "John Locke, Physician and Philosopher"; died Aug. 5, aged 78, of arteriosclerosis.

Macey, Harry Buford ✠ Temple, Texas; born in Lebanon, Tenn., July 9, 1905; University of Tennessee College of Medicine, 1930; entered the Mayo Foundation, Rochester, Minn., as a fellow in orthopedic surgery in January, 1934; became a member of the staff of the Mayo Clinic in the section of orthopedic surgery in January 1936, and was appointed assistant professor of orthopedic surgery in the Mayo Foundation, Graduate School, University of Minnesota; entered the medical corps of the U. S. Navy in 1941 and was separated from active service in 1942 at the U. S. Naval Academy at Annapolis, Md., because of physical disability; specialist certified by the American Board of Orthopaedic Surgery; member of the American Orthopaedic Association, Clinical Orthopaedic Association, American Academy of Orthopaedic Surgeons and the American Association for the Surgery of Trauma; fellow of the American College of Surgeons; on the staff of the Scott and White Clinic; died Aug. 5, aged 46, of coronary occlusion.

Newcomb, William Bradford ✠ Norfolk, Va.; born in Sassafras, Va., in 1886; Johns Hopkins University School of Medicine, Baltimore, 1910; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; past president of the Norfolk County Medical Society; member of the advisory board of Selective Service during World War I; senior surgeon in the U. S. Public Health Service reserve; a member of the Norfolk General Hospital attending staff, of which he had been president; affiliated with De Paul and Leigh Memorial hospitals; died Aug. 1, aged 65, of congestive heart failure.

Snyder, Harvey Welton ✠ Denver; Emory University School of Medicine, 1916; certified by the National Board of Medical Examiners; formerly secretary of the Colorado Board of Medical Examiners and Civil Service commissioner; served overseas during World War I; fellow of the American College of Surgeons; affiliated with Mercy, St. Luke's, Presbyterian, St. Joseph's, St. Anthony, and Children's hospitals; consulting surgeon, Veterans Administration; died in St. Luke's Hospital Aug. 5, aged 62, of pneumonia with complications resulting from a fire in his apartment.

Ackerman, John, Erie, Pa.; Medico-Chirurgical College of Philadelphia, 1897; member of the American Medical Association; for many years on the staff of the Hamot Hospital; died Aug. 8, aged 80, of coronary occlusion.

Ashworth, Lewis Neff ✠ Connersville, Ind.; Indiana University School of Medicine, Indianapolis, 1925; served with American Expeditionary Forces overseas during World War I; president of the Fayette-Franklin Counties Medical Society; second vice-president of Fayette Memorial Hospital; died in Methodist Hospital, Indianapolis, Aug. 3, aged 55, of carcinoma of the esophagus.

Bennett, Carroll Graves ✠ Martinsville, Va.; Medical College of Virginia, Richmond, 1928; on the staff of the Martinsville General Hospital, where he died Aug. 10, aged 47, of coronary disease.

Blaize, Joshua L., New Castle, Ind.; Kentucky School of Medicine, Louisville, 1907; member of the American Medical Association; had been both Knox County clerk and coroner of Knox County; served on the staff of the Indiana Village for Epileptics; affiliated with Henry County Hospital; died in Freeman Greene County Hospital in Linton, Aug. 8, aged 69, of heart disease.

Bloxsom, Paul W. ✠ Grand Rapids, Mich.; Detroit College of Medicine and Surgery, 1917; served during World War I; since 1939 county coroner and medical examiner; affiliated with Blodgett Memorial and St. Mary's hospitals; died in University Hospital, Ann Arbor, Aug. 13, aged 58, of coronary thrombosis.

Burns, Walter Linn ✠ Lynn, Mass.; Harvard Medical School, Boston, 1904; formerly health commissioner of Lynn; died in Lynn Hospital Aug. 17, aged 73, of uremia.

Busch, George C., Chicago; Rush Medical College, Chicago, 1899; died Aug. 13, aged 72, of cerebral hemorrhage, and carcinoma of the colon.

Clark, Charles Patton, Summit, N. J.; Rush Medical College, Chicago, 1904; retired in 1947 after 31 years as medical director of the Mutual Benefit Life Insurance Company in Newark; died Aug. 28, aged 71, of heart disease.

Covert, John De Lamater ✠ Fort Worth, Texas; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1899; died in All Saints Hospital Aug. 3, aged 74, of pulmonary embolism.

Gaskel, Jerome C. ✠ Williamson, W. Va.; Duke University School of Medicine, Durham, N. C., 1933; certified by the National Board of Medical Examiners; served during World War II; died Sept. 4, aged 43, as a result of an accidental discharge of a pistol.

Harber, George Dillard, Chicago; Emory University (Ga.) School of Medicine, 1933; member of the American Medical Association; died Aug. 4, aged 43, of coronary thrombosis and hypertension.

Hutchinson, William Blake ✠ Cleveland; Ohio State University College of Medicine, Columbus, 1922; on the staff of St. Luke's Hospital; died in Shaker Heights, Ohio, July 26, aged 54.

Keefe, Thomas Leo ✠ Logansport, Ind.; Harvard Medical School, Boston, 1928; certified by the National Board of Medical Examiners; served during World War II; on the staffs of St. Joseph's and Memorial hospitals; died in St. Mary's Hospital, Rochester, Minn., Aug. 21, aged 50.

Kistner, John Wesley, Elkhart, Ind.; Rush Medical College, Chicago, 1902; member of the American Medical Association; affiliated with Elkhart General Hospital; died Aug. 13, aged 74, of coronary sclerosis.

Klemm, John William, Washington, D.C.; Columbian University Medical Department, Washington, D. C., 1890; died Aug. 28, aged 93.

Lacey, William Andrew ✠ Havre, Mont.; St. Louis University School of Medicine, 1926; past president of the Hill County Medical Society; died in Sacred Heart Hospital Aug. 7, aged 51, of coronary disease.

Landy, Abraham ✠ New York; Cornell University Medical College, New York, 1920; associate clinical professor of medicine, New York Medical College, Flower and Fifth Avenue Hospitals; on the staff of Morrisania City Hospital; died Aug. 27, aged 56, of coronary occlusion.

Lannon, Paul Callaghan, Honesdale, Pa.; Georgetown University School of Medicine, Washington, D. C., 1927; past president of the Wayne County-Pike Medical Society; served during World War I; died in St. Joseph's Hospital, Carbondale, Aug. 10, aged 52, of carcinoma of the rectum.

Leonard, William H., Maplewood, N. J.; New York Homeopathic Medical College and Hospital, New York, 1891; died Aug. 25, aged 83, of metastatic carcinoma of the liver.

Ludwig, Alex E., Chicago; Chicago Homeopathic Medical College, 1901; died Aug. 17, aged 73, of pneumonia and arteriosclerosis.

McGrew, Donald John ✠ Lake Forest, Ill.; Loyola University School of Medicine, Chicago, 1932; past president of the Lake County Medical Society; past president of the board of health; member of the school board; affiliated with Victory Memorial and St. Therese's hospitals in Waukegan and Lake Forest Hospital, where he died Aug. 8, aged 51, of carcinoma.

McGuire, James Patrick, Chicago; Loyola University School of Medicine, Chicago, 1928; member of the American Medical Association; served during World War II; died in Wesley Memorial Hospital Aug. 18, aged 47, of cirrhosis of the liver.

McQueen, Thomas Gamble, Mifflinburg, Pa.; University of Cincinnati College of Medicine, 1929; member of the American Medical Association; president of the school board; on the staff of Evangelical Hospital; died July 23, aged 50, of coronary occlusion.

McWilliam, John Malcolm ✠ Toledo, Ohio; University of Western Ontario Faculty of Medicine, London, Ont., Canada, 1927; served during World War II; died in Mercy Hospital Aug. 16, aged 50, of acute coronary occlusion.

Mansuy, John Louis, Ralston, Pa.; College of Physicians and Surgeons, Baltimore, 1897; member of the American Medical Association; past president of the Lycoming County Medical Society; served as president of the county and city boards of education; formerly health officer of Lycoming County; chairman of the board of the First National Bank of Ralston; died Aug. 11, aged 81, of cerebral thrombosis.

Markley, Joseph Alexander, Morgantown, W. Va.; Medical College of Virginia, Richmond, 1931; member of the American Medical Association; served in the U. S. Public Health Service during World War II; formerly health officer of Duval County, Fla., and health officer for the West Virginia State Department of Health, with headquarters at Charleston and later at Weston; died Aug. 13, aged 47, of injuries received in a fall.

Martin, Niles, Philadelphia; Medico-Chirurgical College of Philadelphia, 1914; formerly physician for the board of health; served on the staffs of St. Agnes and Hahnemann hospitals; died in Philadelphia General Hospital July 28, aged 66, of arteriosclerotic heart disease.

Miller, George William ✠ Cincinnati; Medical College of Ohio, Cincinnati, 1903; during World War II was given the Civilian Meritorious Award for his service at the Army Induction Center; for many years on the staff of Cincinnati General Hospital; affiliated with Deaconess Hospital and Jewish Hospital; died Aug. 11, aged 70, of cerebral hemorrhage, arteriosclerosis, and hypertension.

Miller, Ormun Durell, Clearwater, Fla.; Ohio State University College of Medicine, Columbus, 1927; member of the American Medical Association and the Ohio State Medical Association; formerly practiced in East Canton; died in Odessa July 25, aged 52, of coronary heart disease and arteriosclerosis.

Mitchell, Hugh Johnson ✠ Fredericksburg, Ohio; Western Reserve University School of Medicine, Cleveland, 1929; died July 30, aged 48.

Mitchell, Joseph Ernest ✠ Washington, D. C.; Columbian University Medical Department, Washington, 1903; served on the faculty of his alma mater, now known as George Washington University School of Medicine; died Aug. 5, aged 80, of arteriosclerosis.

Moll, Gustavus W. ✠ Escanaba, Mich.; Detroit College of Medicine, 1897; past president and secretary of the Delta County Medical Society; served on the staff of St. Francis Hospital; died in Detroit Aug. 9, aged 78, of arteriosclerosis.

Morton, Edward Lee, Hennepin, Okla.; University of Arkansas School of Medicine, Little Rock, 1906; died July 27, aged 74, of heart disease.

Murphy, Norman Dwight, Bangor, Mich.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1904; served during World War I; died July 17, aged 75.

Myers, Samuel Monteith ✦ Corning, Kan.; Central Medical College of St. Joseph, Mo., 1896; affiliated with Seneca (Kan.) Hospital; died in Fort Dodge, Iowa, Aug. 18, aged 74, of injuries received in an automobile accident.

Neafsey, Thomas Michael, Flushing, N. Y.; New York University Medical College, New York, 1898; died Aug. 14, aged 74.

Nettles, Robbins ✦ Ocala, Fla.; University of Alabama School of Medicine, 1911; served during World War I; on the staff of Munroe Memorial Hospital, where he died July 21, aged 63, of acute coronary occlusion.

Nichols, William Edward, Hammond, Ind.; Rush Medical College, Chicago, 1894; member of the American Medical Association; secretary of the Lake County Medical Society; served during World War I; affiliated with St. Anthony's Hospital in Terre Haute and St. Margaret Hospital; died July 21, aged 79, of arteriosclerosis and heart disease.

Nourse, Leslie Myron, Des Moines, Iowa; Drake University College of Medicine, Des Moines, 1908; member of the American Medical Association; affiliated with Broadlawns, Iowa Lutheran, Mercy, and Iowa Methodist hospitals; served as president of the Polk County Federal Savings and Loan Association; died Aug. 15, aged 79, of cerebrovascular accident.

Pearce, William Herbert ✦ Baltimore; University of Maryland School of Medicine, Baltimore, 1891; formerly on the faculty of the Maryland Medical College; past president of the Baltimore City Medical Society; served on the staffs of the Union Memorial and Mercy hospitals; past president of the University of Maryland School of Medicine Alumni Association; died July 28, aged 80, of coronary occlusion.

Pomeranz, Raphael ✦ Newark, N. J.; born in Poland Dec. 10, 1895; Medizinische Fakultät der Universität, Wien, Austria, 1922; specialist certified by the American Board of Radiology; member of the Radiological Society of North America and the American College of Radiology; past president of the New Jersey Radiological Society; served during World War II; affiliated with Newark Beth Israel Hospital, Newark City Hospital, Lutheran Hospital, and the Hospital for Crippled Children; died in Maplewood Aug. 20, aged 55, of multiple myeloma.

Puncheon, William Spouart, Brilliant, Ohio; Ohio State University College of Medicine, Columbus, 1917; member of the American Medical Association; served during World War I; affiliated with Gill Memorial and Ohio Valley hospitals in Steubenville; died Aug. 1, aged 66, of hypernephroma with metastases to the lungs.

Rappaport, Barneth Jackson, Brooklyn; Long Island College Hospital, Brooklyn, 1910; member of the American Medical Association; affiliated with Wyckoff Heights and Beth Moses hospitals; for many years physician for the Metropolitan Life Insurance Company; died Sept. 2, aged 64, of cerebral hemorrhage.

Richards, Rowland, Laguna Beach, Calif.; Columbia University College of Physicians and Surgeons, New York, 1930; served during World War II; died Aug. 20, aged 48, of heart disease.

Robbins, J. Holden ✦ Madison, Wis.; University of Pennsylvania School of Medicine, Philadelphia, 1926; assistant professor of anatomy at University of Wisconsin Medical School; served during World War I; formerly member of the board of education; member of the board of health; on the staffs of Madison General and St. Mary's hospitals; died Aug. 11, aged 52, of coronary thrombosis.

Russell, Charles Luther, Cherokee, Kan.; University Medical College of Kansas City, Mo., 1905; died in Pittsburg, July 30, aged 72, of cirrhosis of the liver.

Schall, David Horace, Barto, Pa.; Jefferson Medical College, Philadelphia, 1901; died Aug. 5, aged 76, of heart disease, chronic colitis, and acute gastritis.

Scott, Robert McKay, Sacramento, Calif.; Washington University School of Medicine, St. Louis, 1944; member of the American Medical Association; specialist certified by the American Board of Pediatrics; served during World War II; on the staffs of the Sutter General, Mercy, and Sacramento County hospitals; died Aug. 1, aged 31, of injuries received in an airplane crash.

Shields, Frederick Brooke ✦ Victoria, Texas; Missouri Medical College, St. Louis, 1899; vice-president of the Texas State Medical Association in 1938; past president of the Victoria-Calhoun-Goliad Counties Medical Society; member of the Radiological Society of North America; formerly city and county health officer; on the staff of Victoria Hospital; division surgeon for the Galveston-Harrisburg and San Antonio Railroad for many years; since 1944 surgeon for the Missouri Pacific Railroad; died June 18, aged 75, of carcinoma of the tongue.

Stroud, James Reaves, Jersey City, N. J.; Howard University College of Medicine, Washington, D. C., 1904; died July 25, aged 76, of carcinoma of the prostate.

Stuart, Carroll W., Chicago; University of Illinois College of Medicine, Chicago, 1930; member of the American Medical Association; served during World Wars I and II; also a dentist; affiliated with Cook County, Grant, and Oak Park (Ill.) hospitals; on the consulting staff of Garfield Park, McNeil Memorial, and Augustana hospitals; died July 1, aged 61, of myocardial infarction.

Sturhahn, Ferdinand O., Webster Groves, Mo.; St. Louis College of Physicians and Surgeons, 1891; member of the American Medical Association; in 1943 was honored by the St. Louis Medical Society for having practiced 50 years; died July 20, aged 86, of gastroenteritis.

Stusser, Samuel, Seattle; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, Chicago, 1912; member of the American Medical Association and the American Society of Anesthesiologists; on the staff of Providence Hospital, where he died Aug. 6, aged 62, of cardiac failure.

Sykes, John Winfield, Avalon, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1921; on the staff of the Women's Homeopathic Hospital for many years; died in Burdette Tomlin Hospital at Cape May Court House, Aug. 5, aged 54, of cerebral hemorrhage and arteriosclerosis.

Taylor, Gardiner Pratt, Columbia, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1904; member of the American Medical Association; for many years school director; formerly coroner's physician; deputy coroner at the time of his death; on the staff of Columbia Hospital; died July 31, aged 70, of coronary occlusion.

Taylor, John Hamilton, Chattanooga, Tenn.; Chattanooga Medical College, 1910; member of the American Medical Association; died Aug. 5, aged 68, of coronary thrombosis and arteriosclerosis.

Thach, Andrew Blaine, Nashville, Tenn.; University of Tennessee College of Medicine, Memphis, 1907; member of the American Medical Association; served as chief of staff of health services for the city schools and as member of the county board of election commissioners; affiliated with Mid-State Baptist Hospital, where he died July 27, aged 68, of coronary thrombosis.

Thomson, J. R., Lake Waccamaw, N. C.; University College of Medicine, Richmond, 1899; died July 23, aged 79, of heart disease.

Trice, William Greene ✦ Waco, Texas; Vanderbilt University School of Medicine, Nashville, Tenn., 1900; during World War II served as a medical examiner for Selective Service; physician and surgeon for the Missouri, Kansas-Texas, and the Cotton Belt railroads; died recently, aged 73, of heart disease.

Tubbs, Ray Burney, Russellville, Ark.; Rush Medical College, Chicago, 1901; died July 27, aged 71.

Tyler, Marcellus H., Richmond, Va.; Leonard Medical School, Raleigh, 1909; died July 12, aged 68, of Parkinson's disease.

Wallace, Harry Lee, Cadiz, Ky.; University of Louisville Medical Department, 1911; member of the county board of health; died July 13, aged 66, of leukemia.

Yeagley, James M. ✦ Lancaster, Pa.; Hahnemann Medical College and Hospital of Philadelphia, 1884; on the staff of St. Joseph's Hospital; died July 22, aged 89.

Zink, Henry Felix, Bellaire, Ohio; Cleveland Medical College, Homeopathic, 1891; member of the American Medical Association; died in City Hospital, Aug. 14, aged 84.

GOVERNMENT SERVICES

AIR FORCE

Off-Campus Opportunities in Air University.—Air University, Maxwell Air Force Base, Ala., can arrange for Air University fellowships for recommended doctoral candidates with compensation ranging from $3,100 to $3,825 per year, and also for visiting professorships for postdoctoral research for recommended faculty members on problems of interest to the Air Force, with compensation of about the professor's institutional salary. The arrangement is established between the institution and Air University, not between the individual and Air University. Details of this opportunity can be had from Bulletin 1 which was just issued by Air University and by writing the Commanding General, Air University, Maxwell Air Force Base, Ala.: Attention: Air University Secretary.

DEPARTMENT OF DEFENSE

Tour of Medical Installations.—A tour of U. S. Armed Forces medical installations to obtain suggestions for improving military medicine will be made during September and October by Dr. W. Randolph Lovelace II, chairman of the Armed Forces Medical Policy Council; Dr. C. W. Mayo, Rochester, Minn., a member of the Citizens Advisory Committee on Armed Services Training Installations; and Dr. Leonard A. Scheele, Surgeon General, U. S. Public Health Service, who will accompany Drs. Lovelace and Mayo as far as Tokyo.

The group will study current treatment and care of wounded and sick military personnel together with related public health problems. They will visit Alaska, Japan, Korea, Thailand, Arabia, Turkey, North Africa, France, Germany, Sweden, and England. The visit to Sweden will be to study the Swedish research program being conducted in Stockholm hospitals. In Korea, Dr. Lovelace and his associates will see patients and inspect field medical equipment. A particular study will be made of evacuation of the wounded by air.

PUBLIC HEALTH SERVICE

Dr. Bailey Appointed Director.—Dr. Pearce Bailey has been appointed director of the National Institute of Neurological Diseases and Blindness which was established by an Act of Congress last summer as one of the National Institutes of Health. Dr. Bailey will initiate a research program on neurological and sensory disorders for which science has not yet found either all the causes or the cures—epilepsy, cerebral palsy, multiple sclerosis, glaucoma, and cataracts. From 1946 to the present, he was chief of the Veterans Administration's Section on Neurology and from 1948 was also assistant chief of the Veterans Administration's Psychiatry and Neurology Division. He was professor of clinical neurology at Georgetown University. He is president of the American Academy of Neurology, and served as United States delegate to the International Poliomyelitis Congress, New York, 1948, and to the Fourth International Neurological Congress, Paris, 1949.

Fluoridation of Water Supplies.—The number of cities adding sodium fluoride to their water supplies in order to effect a 65% reduction in tooth decay has more than doubled during the past year according to the Division of Dental Public Health. In this October there were 121 communities with fluoridation programs in effect, as compared with 50 communities at the same time a year ago. An additional 138 communities have approved a fluoridation program. The programs are either in effect or have been approved in 43 states and the District of Columbia and involve an estimated 11,700,000 persons. Communities with fluoridation programs now in effect range from towns of about 500 population—such as Gearhart, Ore., and Cambridge, Wis.—to cities of more than 100,000—such as Madison, Wis.; Corpus Christi, Texas; Grand Rapids, Mich., and Charlotte, N. C.

The following cities are among those that have approved a fluoridation program, but are not actually adding the compound to their water supplies at present: San Francisco, Baltimore, Louisville, Washington, D. C., Cleveland, Cincinnati, Toledo, Youngstown, Akron, Milwaukee, Pittsburgh, Seattle, and Shreveport, La.

Health Workers from Thailand.—Thirty physicians, nurses, pharmacists, and other health workers have arrived from Thailand for one year of advanced training under programs supervised by the Division of International Health of the Public Health Service. They are the first to arrive of some 59 specialists in that country who have been awarded fellowships under a program sponsored by the Economic Cooperation Administration in collaboration with the Government of Thailand. Twelve of the group now here are physicians; all are graduates of Siriraj Medical School, Chulalongkorn University, Bangkok. There are two women in the group, Drs. Ladda Sinhaseni and Prayoon Tanbiroj.

VETERANS ADMINISTRATION

Residencies in Neurology.—Residencies in medical neurology are available at the United States Veterans Administration Hospital, Hines, Ill., beginning Jan. 1, 1952, for a period of three years. The residency program is under the direction of the Department of Nervous and Mental Diseases, Northwestern University Medical School. The training is fully accredited by the American Board of Psychiatry and Neurology.

MISCELLANEOUS

Coal Mine Fatality Rate Up Slightly.—Secretary of the Interior Oscar L. Chapman declared Oct. 2 that the average monthly fatality rate in American coal mines during the first eight months of this year is slightly higher than in the years 1949 and 1950. For all coal mines, a Bureau of Mines report shows the average monthly rate from January to Sept. 20 was 0.95 fatalities per million man-hours of exposure, compared with monthly average rates of 0.91 and 0.90 in 1949 and 1950, respectively, the Bureau of Mines stated. The greatest increase was in Pennsylvania anthracite mines, where the average monthly rate for the first eight months was 0.97 per million man-hours, compared with 0.85 in 1949 and 0.75 in 1950. The fatality rate in bituminous-coal and lignite mines also was up slightly, the monthly average being 0.94 per million man-hours for the first eight months of this year, compared with 0.92 in 1949 and 0.93 last year. Analyses of the principal causes emphasize the need for unceasing vigilance on the part of everyone engaged in mining coal, from top management to the youngest miner. Secretary Chapman said that the record is all the more disappointing because we know that coal mining can be much safer than it is now, as witness the long periods of injury-free operation of many individual mines.

Trend in Coal-Mine Fatalities and Fatalities per Million Man-Hours of Exposure in the Nation's Coal Mines

	Bituminous		Anthracite		All Coal	
Calendar Year	Fatalities	Rate	Fatalities	Rate	Fatalities	Rate
Monthly average 1949..	42	0.92	8	0.85	50	0.91
Monthly average 1950..	46	0.93	8	0.75	54	0.90
August 1951.....	49	0.87	7	0.78	56	0.86
Monthly average 1951.. (8 months)	49	0.94	8	0.97	57	0.95

The accompanying table shows the trend in coal-mine fatalities and the number of fatalities per million man-hours of exposure in the nation's coal mines, 1950 and 1951 figures being subject to revision.

FOREIGN LETTERS

LONDON

Annual Representative Meeting of British Medical Association.—The Annual Representative Meeting was held in the Great Hall of B. M. A. House, London, June 13-16. Dr. J. A. Brown, a physician of Birmingham, was chairman. Other officials were Dr. A. W. Sichel of Capetown, president-elect; Dr. E. A. Gregg, chairman of the council; Sir Henry Cohen, president, and Mr. A. M. A. Moore, treasurer. Dr. Gregg noted that this was the first Annual Representative Meeting since the departure of Dr. Charles Hill from the secretaryship. Dr. Hill was for many years secretary of the British Medical Association. He was well known to the lay public as the "radio doctor." His election to Parliament as a Conservative member for Luton in the last general election had necessitated his relinquishing the secretaryship of the medical association.

The Reviewing Committee.—Dr. Barbara Abercromby of Liverpool said that there are still many men of consultant standing and doing consultant work who, after three years, have not yet been given the official status of consultant in the National Health Service. The Ministry of Health promised a review of their position, terms of service, and remuneration before the end of 1951, and she moved that, in fairness to the applicants, the majority of the members of the new committee to review their position should consist of persons who had not assessed their grading on previous occasions. Mr. A. Lawrence Abel, a surgeon and member of the council of Marylebone, London, supporting the motion, said that he knew cases of senior men, well respected in the profession, who had been the only surgeon of a hospital or the senior surgeon of a big hospital, and had been for three years designated as "senior hospital medical officers" and not as consultant, simply because they were also general practitioners. He had spoken on their behalf on many occasions, but the injustice to them still continued. The representative body had been given a promise that all senior hospital medical officers who wished to appeal would be regraded during 1951, but this had not been done.

Dr. G. L. Barber of mid-Essex, in moving that the strongest support should be given to the Joint Committee's representations to the Ministry with regard to the appointment of hospital consultants, said that danger was now apparent in the machinery for their appointment. The Ministry had made a regulation that allowed many lay members to adjudicate on the qualifications of a consultant. Dr. Rowland Hill said the Joint Committee had fallen "just short of fisticuffs" with the Ministry of Health officers on this point. The motion was carried.

Family Doctor Remuneration.—Dr. Wand, chairman of the General Medical Services Committee, on the subject of the remuneration claims of family doctors under the National Health Service, stated that a year ago we were engaged in an inquiry into the expenses of practice in order to arrive at a statement of the net incomes of doctors from the National Health Service. At that time the Minister agreed that the Spens Report "remains the basis of the remuneration of general medical practitioners until such time after the usual consultations as some other basis is substituted. He contemplates that any future alteration of remuneration should normally be a matter for negotiation." The conference of representatives of all family doctors in the Health Service took place in March this year. Meanwhile, important changes had occurred. Mr. Bevan left the Ministry of Health; there was also a change in the permanent secretary of the Ministry and a change in the status of the Ministry, in that it no longer dealt with housing.

The doctors' representatives met the Minister on February 28, and, as a result, received a letter indicating that there was a prima facie case for inquiry. The next day the conference, feeling satisfied to receive this type of letter for the first time from the Minister, welcomed the suggestion and authorized the committee to carry out negotiations.

In May this year we received the result of the income tax inquiry into practice expenses. The two sides are still in dispute as to whether there should be a deduction from the gross income of 36.5% or 37.5% for practice expenses. Soon after this the government decided to charge part of the cost of dentures and eye glasses. Then came the national budget and Mr. Bevan's resignation from the government—in fact, almost a government crisis.

As a result of meeting the new Minister it became evident that some new monies would be likely to be available.

On May 9, a six-hour meeting with the Minister revealed three things: First, that the Chancellor of the Exchequer had placed a ceiling of £400,000,000 on the Health Service, (i. e., $1,120,000,000). It will be remembered that the previous year's costs approached $1,400,000,000. Second, the Ministry were concerned to effect a redistribution among the doctors of the total pool of monies. Third, they were anxious to secure a reduction in the bill for drugs. It was proposed that there should be a working party of the two sides of the details of these points.

Correspondence Between Committee and Ministry.—Dr. Wand then quoted letters illustrating the prevarications and difficulties of negotiating with the Ministry of Health. A letter from the Ministry on February 25 said that "the Minister himself is convinced that there is a good prima facie case for reviewing, as a matter of urgency, both the adequacy of the total remuneration of the family doctors and its distribution" and that he would look without delay at the best way of speeding up that review.

To increase the family doctor's remuneration, a sum of £2,000,000 ($5,600,000) was to be taken from general funds allotted to National Health. This sum represented about 11% of present practice expenses, that is, for the year ended March, 1950. Since that time there had been a general increase in costs. The Ministry has undertaken to hold a further inquiry and to bring the figures for expense estimates up to their 1951 level. This further inquiry would doubtless show that practice expenses were not far short of the $5,600,000 offered. If the practice expenses proved to be higher than this sum, family doctors would be actually worse off. This amount represented a maximum offer by the Ministry.

As for the ceiling figure of £400,000,000 ($1,120,000,000) a letter had been published in the lay press; the Minister had stated that he would provide all the hospitals asked for and that he would go on spending as usual on other parts of the service. This would require £423,000,000 ($1,184,000,000). It was obvious that the hospital service must be maintained, and the necessary saving of $644,000,000 must be made by charging for dentures and spectacles. A cut had been made in dentists' remuneration, but, if the accounts presented by dentists were in excess of estimates, it was difficult to see how the government could refuse to pay them. The same applied to pharmacists.

If an epidemic occurred, resulting in the use of a large number of expensive drugs and requiring extra hospital beds, the cost of the hospital service and pharmacy would increase. Everyone except the general practitioner would be doing more work and getting more pay.

As to prescribing costs, it must be remembered that the Minister had said that he would need to be satisfied that the committee was taking all possible steps open to it to eliminate extravagance in prescribing (without detriment to the patient, of course). It was known that the $5,600,000 was contingent on two factors: distribution and the prescribing problem. What would the taking of steps to eliminate extravagance mean in practice? He thought the only possible meaning to be a positive reduction in dispensing costs, owing to the increase in the cost of drugs. On the other hand, they were of great benefit to the patient; in his opinion it was the duty of the doctor to prescribe them. When prescribing, the doctor had to consider whether an

The items in these letters are contributed by regular correspondents in the various foreign countries.

item in a particular prescription would affect his own personal income, and, rightly or wrongly, the public would feel anxious about this.

Niggardly Offer.—It would appear, said Dr. Wand, that the government, having plunged into a comprehensive medical service against the advice of the profession, felt that the family doctors should be the people to carry the burden, and he could not see why the niggardly offer that had been made should be open to the interpretation that the family doctors' remuneration might depend on depriving the patient of necessary medicaments. Usually, he said, doctors were careful when they prescribed. There was disciplinary machinery in existence for dealing with those who were not. The doctors themselves took part in the machinery, and they saw that those who were unnecessarily extravagant in their prescribing had appropriate reductions made in their remuneration. The machinery had been set up a long while ago.

In regard to the committee's claim for more money to be devoted from the Pool to the family doctor, the committee wished to take part in the settlement of this claim, because it would be in the public interest. It was difficult to set a precise figure for the amount of the claim; statements of receipts by doctors up to 1950 were available, but not statements of those receipts up to March, 1951. The number of doctors in March, 1950, was known, but not the number today, and the exact interpretation of the income tax figures for the year ended March, 1950, was still in dispute. The figure in dispute was 1%, but it was not known how much practice expenses had gone up since then.

The committee asked for arbitration on the subject of "betterment" (betterment being an increase in salary proportionate to present day value of money as compared with prewar values). The Spens Committee had stated in its representation that its recommendations would be subject to such betterment, and it was the subject of betterment that concerned the committee; that is, the committee asked that somebody other than the Ministry to determine what the amount of betterment should be. Excluding any reference to extra work, and taking a moderate increase for practice expenses and for betterment, there was no doubt that the claim was several times the amount of the offer made by the Ministry. There had been inquiry after inquiry and delay after delay. There had been mention of wage freezes and ceilings and rearmament. While these disputes were going on, the family doctor continued with his daily work, which bore no relation to hours of work or his physical well-being Now the Ministry offered him a sum that was barely an increase in practice expenses since March, 1950. Such an offer not only reduced the status of the family doctor but caused a serious distrust of him in the public mind.

In conclusion, Dr. Wand said that the committee was recommending that its claim should be put to arbitration and the arbitration must have regard to the change in the value of money since 1939.

Interpretation of Spens Report.—The Spens Report had made its recommendations in net terms and at prewar values. The public does not realize that roughly 40% of a doctor's income goes in expenses. Out of the annual capitation fee of about $2.40, the doctor earns less than 3 cents per week as net remuneration, and this is subject to tax, as is everybody else's remuneration, but his expenses have gone up considerably, and, as the cost of living rises, so the net remuneration goes down. The Spens Report recommended that a certain proportion of doctors should earn upward of $7,000 a year at prewar values. It recommended that there should be an incentive to go into general practice and that a doctor should have a reasonable life, so that he might give his best to the community, with ample opportunity for study and leisure. Whenever we have asked the Ministry what, in their opinion, constitutes Spens remuneration, we have always been refused an answer.

Minister's Responsibility for Future of Family Doctor.—The doctors have always been anxious to discuss with the Ministry the problems, particularly the difficulty of the young man getting into practice and his difficulties after entering; also the question of financial incentive, the need for liaison with the consultants, and the burden of work. We have warned the Minister that there is considerable frustration, that the young man is feeling and saying that he has nothing to strive for, and that the older man with the fairly full list feels that he is being exploited; above all, that the British general practitioner has practiced good medicine in the past and we are anxious that it should remain good. We want the Minister to understand that it is his business to see there is no such frustration in the ranks of family doctors.

The Abandoned South African Visit.—Dr. C. C. Wallace, a physician of Guildford, said he wished to draw attention to the manner in which the decision of the representative body on this subject had been reversed. The representative body, after hearing all the arguments put forward on both sides, had come to a definite conclusion that the Annual Meeting should be held in South Africa. At this point, Dr. Gregg said that he had been in favor of the association's visiting South Africa this year and all the preparations for the visit had been made, but it had been learned that there had been a further development of the government policy in South Africa concerning the admission to the Union of non-Europeans. The medical secretary of the British Medical Association in South Africa had then sought an assurance that no difficulty would be placed in the way of any member of the British Medical Association from any part of the world entering the Union for the purpose of attending the meeting of the association. The Minister of the Interior had been unable to give that assurance, and the council of the association had been reluctantly obliged to come to the conclusion that the proposed visit must be abandoned. They would not allow any member to be subjected to any indignity in South Africa.

ITALY

Academy of Sciences.—At a meeting of the Academy of Sciences of Ferrara, Prof. Coppo lectured on the possible association of atherosclerosis and hypercholesteremia. He emphasized that the pathogenesis of atherosclerosis is a very complicated subject, involving many factors. The speaker and some of his co-workers have studied the importance of a disordered metabolism of lipids and more precisely of cholesterol. It has been demonstrated that in experimental animals myocardial damage is associated with vascular changes. In the clinical field, the relationship between hypercholesteremia and irregularities in electrocardiographic tracings of patients was studied; cases of coronary insufficiency and of myocardial infarction attributable to the hyperlipemia were described; the behavior of the cholesterol relative to the age of the patient was studied. The research led the speaker to believe that at the onset atherosclerosis cannot be distinguished from arteriosclerosis and to favor a unitary pathogenic interpretation, essentially metabolic, of the atherosclerotic process. Because of a predisposing constitution and hereditary traits, a metabolic disorder appears, manifested by persistent hypercholesteremia. Prof. Coppo believes that this condition is sufficient for the appearance of myocardial and arterial lesions. Therefore, according to him, the etiological factors of the atherosclerotic process are initially independent of age.

At another meeting Prof. Rietti discussed the treatment of paroxysmal tachycardia with intravenous injections of massive doses of digitalis. Paroxysmal tachycardia in its various forms (atrial, nodal, and ventricular) differs from the Bainbridge reflex. There are persons who are able voluntarily to accelerate their heart beat; in one of these rare cases the electrocardiogram gave the typical tracing of the Wolff-Parkinson-White syndrome. Cases of paroxsymal tachycardia with precordial pain, lowering of the systolic pressure, transitory rise of temperature, and leukocytosis have been observed; in these cases a differential diagnosis from acute myocardial infarction should be made. In exceptionally severe and prolonged attacks, especially if they occur in persons with valvular defects, intravenous injection of massive doses of digitalis can, according to Bohnekamp, have immediate therapeutic effect, without phenomena of intolerance.

Prof. Quinto reported cases of malignant cancer of the cervical stump observed during the last 10 years in the gynecologic department of the School of Obstetrics in Ferrara. The cases were discussed with respect to diagnosis, prognosis, and con-

ditions that led to surgical intervention; clinical and anatomicopathological characteristics, and therapy were also discussed. Prof. Quinto conceded that the problem of prophylaxis of cancer of the stump must be kept in mind when surgical intervention is performed for benign neoplastic disease or for inflammatory conditions of the uterus and the adnexa. On the basis of the most recent statistics and his practical personal experience, Prof. Quinto favors such intervention, although he admits that definite indications for subtotal hysterectomy must still be established for those cases in which it is convenient to preserve the cervix or even more extensive areas of the portio supravaginalis cervicis, besides the cases in which total hysterectomy is contraindicated. The surgical intervention which, according to the speaker, combines the values of total hysterectomy with those of subtotal hysterectomy, without causing inconvenience, is total intracervical hysterectomy. In his opinion, this is good in prophylaxis of carcinoma of the stump. Prof. Lenzi reported on the diagnosis of endocranial tumors, discussing the prognostic and therapeutic reasons which make the diagnosis important. Clues to diagnosis can be obtained from evaluating the location of the process, pneumoroentgenographic examination, examinations with contrast medium, and the use of radioactive isotopes. The speaker discussed contributions to diagnosis by arteriography which may reveal the principal aspects of displacement, distortion of normal vessels, velocity of circulation, presence of arteriovenous fistulas, and appearance of an enriched vascular network as it occurs in meningeal sarcomas.

Prof. Lenti presented some observations on 11 cases of diabetes mellitus that developed in the course of or soon after acute infectious disease. Five of these cases originated from tonsillitis, five from influenza, and one from infectious hepatitis. Three additional cases of diabetes mellitus, mild and silent at the onset, became severe and chronic after an attack of influenza. On the basis of the clinical, anatomic, and experimental data, the speaker stated that in most cases acute or subacute pancreatitis may be caused by the infectious disease in persons who were otherwise healthy. This concept is of a particular therapeutic interest because prompt management with vigorous dietetic treatment and with insulin might result in great improvement.

YUGOSLAVIA

Heart Surgery in Zagreb.—In July, 1950, a center for cardiology was established at the Medical Faculty, Zagreb, for the examination and treatment of congenital malformations of the heart. The World Health Organization was instrumental in the creation of this center, especially by sending a prominent heart surgery team under Prof. Crafoord, the well-known Swedish surgeon, and Dr. Mannheimer, a prominent pediatrician-cardiologist, and by supplying most of the costly apparatus and equipment.

The Swedish demonstration team stayed a fortnight in Zagreb and performed nine operations. After their departure examination and treatment of congenital malformations were continued in a close collaboration of a team of pediatricians, cardiologists, surgeons and x-ray specialists. In less than a year they have examined over 100 congenital malformations of the heart and performed 25 operations. There were two deaths. In all other cases the results were good. During that period 45 catheterizations of the heart and 30 angiocardiographies were carried out for diagnostic purposes.

The center is interested, also, in acquired heart defects, and makes investigations concerning the pulmonary circulation in some diseases of the lung. Acquired defects treated at the center include 10 cases of mitral stenosis, two of which were fatal.

One of the tasks of the cardiologic team will be to seek out children with congenital malformations of the heart and to make the facilities of the clinic available to them. Mass examination of infants, of children of preschool age, and of school children is planned.

The work at the cardiological laboratory has been greatly facilitated by the fact that all medical members of its staff have, on fellowships granted by the WHO, visited many prominent medical centers in Europe, Canada, and the United States and thus have been able to make first-hand studies of the most modern achievements in their respective specialties.

Institute of Industrial Hygiene.—The Institute of Industrial Hygiene in Zagreb, founded in 1948, is one of the research institutions of the Yugoslav Academy of Sciences and Arts. The present main building of the institute was completed this year and opened on May 1. The laboratories have a total floor space of about 2,000 square meters with about 30 rooms of various sizes. The institute has a small mechanical workshop, established with the aid of the United Yugoslav Relief Fund of America. There is also a library and a lecture room, equipped with all teaching facilities, for about 100 students. The institute is under the executive control of a director, who is responsible to the chairman of the board of the institute. Dr. B. Kesić, associate professor of hygiene and social medicine at the University of Zagreb, was nominated the first director.

The functions of the institute are (*a*) to investigate work conditions and the problems of occupational hygiene in general, especially those in industry; (*b*) to make it possible for the state authorities and all institutions interested to avail themselves of the results of its research work for practical purposes; and (*c*) to spread the knowledge on occupational hygiene.

These functions indicate that the work of the institute should be of two kinds: fundamental research to create a sound scientific basis for field work, including standardization of methods for analysis of the working environment and its control, and methods for the analysis of biological material that serve in the early diagnosis and prevention of occupational diseases. The other part of the work is carried out on request of other government agencies, viz., sanitary inspection for the Ministry of Health and labor inspection for the Ministry of Labor. In addition to these main tasks, the institute takes part in training of industrial health specialists, i. e., industrial physicians and sanitary engineers. The organization of training in these branches of medicine is in the hands of the School of Public Health.

The program of the institute is approved by its Board, which consists of representatives of the Yugoslav Academy, the Ministry of Health, the Ministry of Labor, the Ministry of Industry, and the Medical Faculty of Zagreb. The total staff at present is 43, of whom seven are workers with medical training and 13 with engineering and scientific training.

The equipment of the institute was to a large extent supplied by the United Yugoslav Relief Fund and the Rockefeller Foundation (through the School of Public Health). The work of the institute is organized in four main divisions:

1. *Division of Psychology and Physiology of Work.*—The study of fatigue and recovery after static work forms one of the main research problems of this division, along with the biometric study of school children and the investigation of various psychological and pharmacological stimulants on the work output.

2. *Division of Occupational Pathology.*—Lead poisoning and mercury poisoning are the subject matter of research of this division. All cases of occupational diseases occurring in the territory of Zagreb and P. R. Croatia are registered with and examined by the staff of this division. Research on the role of Heinz bodies in occupational poisonings is also in progress.

3. *Division of Industrial Toxicology.*—This division includes a laboratory for clinical biochemistry, namely, for the analysis of industrial poisons in biological material. There is also a research group studying cancerogenic properties of flax. This division takes part also in the investigations of Heinz bodies and the hematology of lead and mercury poisonings.

4. *Division for Environmental Problems.*—The staff of this division is engaged in standardization of analytical methods of industrial poisons and hazards. The study of environmental conditions in the mercury mines of Idria formed part of its program. The development of a respirator against mercury vapor was also one of the tasks of this division. The determination of tetranitromethane in air was studied recently. There is also some work going on in the field of filters for aerosols.

The results of the researches and field work carried out by the staff of the institute is published in the quarterly *Arhiv za higijenu rada* (Archives of Industrial Hygiene), which is now in its second year of existence. International relations are encouraged. In 1950 a conference on industrial hygiene took place in Zagreb and was attended by several British and Swedish workers in the field of industrial hygiene.

CORRESPONDENCE

BIOCHEMICAL DISTURBANCES IN HYPERTENSION

To the Editor:—The demonstration of a biochemical disturbance is an aid to the understanding of the basic process in any disease. In the disease state of hypertension, there is no agreement as yet on the existence of any such basic disturbance. There is agreement only on the physical disturbance of elevated intra-arterial pressure and the morphological lesions as being fundamental characteristics of the disease process.

Three of the present methods of producing chronic elevation of blood pressure in experimental animals are (1) treatment with high sodium chloride intake plus daily injections of desoxycorticosterone; (2) the production of disturbed renal blood flow by such methods as artificial constriction of the renal artery, as first demonstrated by Goldblatt (Studies on Experimental Hypertension: Production of Persistent Elevation of Systemic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* **59:**347, 1934) or by a tie placed around the kidney; and (3) the removal of both kidneys plus maintenance of the animal by an artificial kidney, as demonstrated by Grollman and co-workers (Role of the Kidney in Pathogenesis of Hypertension as Determined by a Study of Effects of Bilateral Nephrectomy and Other Experimental Procedures on Blood Pressure of the Dog, *Am. J. Physiol.* **157:**21, 1949).

All these procedures cause elevation of blood pressure, and they also produce lesions similar to those occurring in patients with high blood pressure. Evidence for further similarity in these conditions, namely, the biochemical disturbance of an increased intracellular sodium level and a low intracellular potassium level, has been demonstrated by the first two methods mentioned above and probably can be found in the third method.

Desoxycorticosterone injections, plus a high sodium chloride intake, have been shown (Buell, M. V., and Turner, E.: Cation Distribution in Muscles of Adrenalectomized Rats, *Am. J. Physiol.* **134:**225, 1941. Miller, H. C., and Darrow, D. C.: Relation of Serum and Muscle Electrolyte, Particularly Potassium, to Voluntary Exercise, *Am. J. Physiol.* **132:**801, 1941. Ferrebee, J. W., and others: Certain Effects of Desoxycorticosterone: Development of "Diabetes Insipilus" and Replacement of Muscle Potassium by Sodium in Normal Dogs, *Am. J. Physiol.* **135:**230, 1941. Darrow, D. C.; Schwartz, R.; Iannuci, J. F., and Coville, F.: Relation of Serum Bicarbonate Concentration to Muscle Composition, *J. Clin. Invest.* **27:**198, 1948) to produce this disturbance in skeletal muscle. Darrow and Miller (Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate, *J. Clin. Invest.* **21:**601, 1942) found similar changes in cardiac muscle, and Eichelberger (Distribution of Water and Electrolytes Between Blood and Skeletal Muscle in Experimental Hypertension, *J. Exper. Med.* **77:**205, 1943) showed the same disturbance in the muscles of dogs made hypertensive by constriction of the renal artery. Although she notes that most of the increase in sodium per wet weight of skeletal muscles is due to an increase in the relative volume of the extracellular fluid, when one calculates the intracellular sodium by accepted methods, there is an equivocal rise in intracellular sodium. However, the lowering of potassium is sufficient to be significant statistically. Laramore and Grollman (Water and Electrolyte Content of Tissues in Normal and Hypertensive Rats, *Am. J. Physiol.* **161:**278, 1950) repeated this work, analyzing seven different tissues in rats made hypertensive by a tie on one kidney, plus, on occasions, contralateral nephrectomy. While the data presented are not sufficient to check the intracellular sodium content by calculation, the authors conclude that it shows that sodium entered the cells. Their data also demonstrated a decrease in tissue potassium.

Again, the animals in which bilateral nephrectomy was performed, and which were maintained in electrolyte balance by use of the artificial kidney every third day, showed a fall in plasma sodium (Vanatta, J.; Muirhead, E. E., and Grollman, A.: Improvements on Artificial Kidney: Experimental Study on Its Application to Dogs Bilaterally Nephrectomized or Otherwise Deprived of Renal Function, *Am. J. Physiol.* **156:**443, 1949). As the dogs did not always gain weight, vomit, or have diarrhea, this suggests the transfer of sodium into the cells. Unfortunately, tissue analyses of these animals are not available for checking this possibility nor for evaluation of intracellular potassium.

If procedures that are known to decrease intracellular sodium and increase intracellular potassium were to cause improvement in the clinical state of the patient, this would constitute indirect evidence supporting the theory. Darrow showed that a low sodium diet causes a decrease in intracellular sodium and an increase in intracellular potassium in normal experimental animals, as determined by direct analyses of skeletal muscle. Of course, such a diet is known to be effective therapy in a significant number of patients with hypertension. Bryant (Effect of Potassium on Ventricular Deflections of Electrocardiogram in Hypertensive Cardiovascular Disease, *Proc. Soc. Exper. Biol. & Med.* **67:**557, 1948) demonstrated that electrocardiographic abnormalities associated with hypertension in man could be changed toward normal not only by a low sodium diet but by a high potassium diet as well. Such changes were produced 25 times, in successive experiments, although these changes occurred spontaneously in only 10 to 20% of patients (Watkins, D. M.; Froeb, H. F.; Hatch, F. T., and Gutman, A. B.: *Am. J. Med.* **9:**428, 1950) observed for long periods. In McQuarrie's patient with hypertension associated with excessive sodium intake, hypertension was not induced by sodium unless potassium intake was minimal. (In Bell, E. T.: Hypertension: A Symposium Held at the University of Minnesota on Sept. 18, 19, and 20, 1950. Minneapolis, University of Minnesota Press, 1951, pp. 517-520.) He states that "one part of potassium appears to be sufficient to nullify the hypertensive effect of several chemically equivalent amounts of sodium."

Since there is direct analytical evidence that the sodium content of cells is increased and the potassium content decreased, in animals made hypertensive by desoxycorticosterone plus sodium chloride, or by interference with renal blood flow, and there is indirect evidence of this in animals made hypertensive by nephrectomy, and in clinical patients, it is suggested that this might be a fundamental chemical disturbance of this disease state.

JOHN C. VANATTA, M.D.
Southwestern Medical School of the University of Texas
2211 Oak Lawn Ave., Dallas, Texas.

LEUKEMIA AND OTHER MALIGNANT DISEASES IN PHYSICIANS

To the Editor:—According to Dublin and Spiegelman (1948), and March (1950), leukemia causes death 8 to 9 times oftener in radiologists than in all other physicians. It is also a more frequent cause of death in dermatologists. To determine whether physicians are an example of the rule of inverse association under additional exposure (Peller), second, whether and to what extent fluoroscopy endangers the general practitioner and internist, and, third, how soon the danger of leukemia becomes manifest, we surveyed the necrologies published in THE JOURNAL from June 1, 1947, to June 1, 1951. The cause of death is listed for 9,354 physicians (no cause is given in 2,568). Among them are 111 deaths from leukemia and 1,134 from other malignant diseases. The ratio of all deaths from malignant diseases to all deaths (with given cause) is thus 13.2% as compared with 14% for all white males who in 1947 died at the age of 25 or more.

Physicians have in all age groups increased ratios of leukemia. In the five year age groups between 25 and 44, leukemia accounts in physicians for 70.0, 33.3, 22.3, and 22.6%, respectively, of all fatal malignant diseases and for 14.4, 15.8, 7.9, and 5.7% in all white males (1947). Later, in the age groups 45-54, 55-64, 65-74, 75-84, and 85 and over, the percentages of leukemia are

8.7, 9.3, 7.8, 5.8, and 8.0, respectively, versus 4.5, 3.3, 2.9, 2.2, and 1.6%.

Physicians also have higher ratios of leukemia to all deaths (with listed cause) than encountered in all white males. Most pronounced is this difference at 25-29 years, the ratio being 8.4±3.0 versus 0.9%, whereas in the other age groups the proportion is between 4:1 (in lower age groups) to 2:1 (in higher age groups).

Since within the age group 35-74 there is hardly any difference between the age-adjusted total mortality of physicians and the white male population, elevated ratios of leukemia imply a similarly increased mortality from this disease. In physicians, leukemia mortality is increased within the first five years of exposure. Obviously, the latency period is short or shortened in persons in whom, without x-ray exposure, either the same disease (leukemia) or another malignant disease would have later developed. The latency period is shorter than it is, for instance, in miners of Joachimsthal, in whom radium induces lung cancer (Peller, 1938), or in dial painters' bone sarcomas (Hoffman and Martland, 1926).

Turning to nonleukemic malignant diseases we find their ratios to all deaths from known cause to be low in physicians who died at 25 to 29 and between 40 and 74 years, i. e., 3.6, 9.1, 11.7, 11.3, and 13.5%, respectively, in physicians, versus 5.4, 10.1, 13.3, 16.0, and 15.6% in all white males. In the age groups 30-39 and 75 and over, physicians have higher ratios.

When all malignant diseases are considered together, we encounter an interesting pattern in the changes of age-specific ratios. In physicians who died at 25 to 44 as compared to all white males in this age group the excess in the ratio of malignant diseases gradually diminishes: 12.0±3.5 versus 6.3%, 12.5 versus 7.6%, 11.5 versus 8.9%, and 11.8 versus 10.8%. At the age of 45, the higher number of deaths from malignant diseases in physicians vanishes and becomes lower than that for all white males in the three age groups between 45 and 74 years: 12.8 versus 13.9%, 12.5 versus 16.5%, and 14.6 versus 16.0%. Then, the relationship becomes once more reversed: 13.8% for physicians versus 12.9% for all white males, and in the highest age group, 8.4 versus 7.7%.

Combining our data with those of Dublin and Spiegelman, we conclude that in the age group of 40-74 physicians have a leukemia mortality more than twice increased, a mortality from all other malignant diseases about 15% below the level of all white males (1947), and a total mortality from malignant diseases 10% below that level. The highly increased ratios of leukemia in the 25-39 year groups do not leave any doubt that also in these young physicians leukemia mortality is considerably increased.

The lack of deaths due to nonleukemic cancers is only to a small extent explained by better therapy. We correlate this deficit in the age group 40-74 with (1) precipitated manifestation of leukemia and other malignant diseases (because of the x-rays), (2) delayed manifestation of a number of nonleukemic cancers (because of social conditions), and (3) with an assumed relative preponderance of surface cancers, which are less fatal, over internal cancers.

Radiologists and dermatologists are not the only physicians who show a high incidence of leukemia. Considering the numerical strength of these two groups of specialists and their ratio of leukemia, we estimate that in physicians who died at from 35 to 74 years of age and were neither radiologists nor dermatologists, the ratio of leukemia is 1.14% as compared with 0.56% in all white males (1947). Probably this increased risk is due to the fluoroscopic work of general practitioners and internists.

The more American physicians make use of fluoroscopy in their offices the more mortality from leukemia is bound to increase. This danger might be lessened or even eliminated if steps were taken to adapt the fluoroscopic attire to the need of better protection. Perhaps the American Medical Association could take the initiative.

SIGISMUND PELLER, M.D.
164 E. 81st St., New York 28.
PAUL PICK, M.D.
983 Park Ave., New York 28.

VITAMIN B_{12} IN THE TREATMENT OF MULTIPLE SCLEROSIS

To the Editor:—Because of conflicting reports in the literature (Lereboullet, J.; Pluvinage, R., and Coty, R.: Vitamin B_{12} in Multiple Sclerosis, *J. A. M. A.* **143:**1272 [Aug. 5] 1950. Schumacher, G. A.: Treatment of Multiple Sclerosis, *J. A. M. A.* **143:**1241 [Aug. 5] 1950) regarding the effectiveness of vitamin B_{12} in the treatment of multiple sclerosis, we undertook a study, on the basis of thorough history and neurologic and laboratory examinations, of 24 patients in whom a diagnosis of multiple sclerosis was considered justifiable. Of these, six were treated in the hospital and 18 in the outpatient department. The six hospitalized patients received 100 micrograms of vitamin B_{12} intramuscularly every other day for a three-month period. Of this group, five received 1,000 micrograms every other day for an additional three-month period. Fifteen outpatients received 100 micrograms three times a week for three months. Two outpatients received 1,000 micrograms three times a week for three months. Three outpatients have received 1,000 micrograms three times a week for two months, and therapy is continuing. During this course of therapy, neurologic examinations were performed on all patients at monthly intervals.

Approximately one-fourth of the patients observed an increase in appetite and a sense of well-being. There was, however, no objective evidence of neurologic improvement, aside from such fluctuation as might be expected in the natural course of the disorder.

Two patients maintained after cessation of the treatment that they felt much stronger and were definitely benefited by administration of vitamin B_{12}. For this reason they were given placebos for two months while under the belief that they were being treated with vitamin B_{12}. They have reported the same dramatic improvement with the placebo as they maintained for vitamin B_{12}. There was no objective evidence of change in these patients.

Since the beginning of this investigation, Simson, Herfort, Krim, and Meyer (Effects of Vitamin B_{12} in Multiple Sclerosis, *Proc. Soc. Exper. Biol. & Med.* **75:**721 [Dec.] 1950) have published a report, the results of which are comparable to ours.

It is concluded that vitamin B_{12} is not effective in the treatment of multiple sclerosis.

CARL B. BOOTH, M.D.
TIFFANY LAWYER JR., M.D.
THEODORE J. C. VON STORCH, M.D.
Montefiore Hospital
New York 67.

TRIETHYLENE MELAMINE IN LEUKEMIA

To the Editor:—The material in the article by Kravitz, Diament, and Craver on the use of triethylene melamine in leukemia, in THE JOURNAL, Aug. 25, 1951, page 1595, was contrary to my experiences.

Hyperuricemia, uremia, and a lower-nephron-nephrosis-like syndrome are not infrequently seen in leukemia. In the last months two patients with leukemia were seen who showed these abnormal chemical findings. The blood urea values on admission were 50 mg. per 100 cc. and rose to 250 mg., while the uric acid values ranged from 5 to 22 mg. The intravenous urogram and retrograde urogram failed to reveal any abnormalities in the early phases. The kidneys were of normal size. Gout symptoms became manifest in both patients. The kidneys increased in size as the uremia and hyperuricemia became worse. Triethylene melamine, 1 mg. daily, and colchicine, 1/100 grain (0.60 mg.), were given each patient three times daily by oral administration. The urea diminished to below 50 mg., and the uric acid values fell to between 3 and 4 mg.

I might suggest that the dosage administered by the Memorial group was too large. In the past year I have seen five patients with Hodgkin's disease and seven patients with leukemia who have been maintained in a satisfactory remission by oral administration of 0.25 mg. to 1 mg. daily.

PERK LEE DAVIS, M.D.
255 S. 17th St., Philadelphia 3.

BUREAU OF LEGAL MEDICINE AND LEGISLATION

MEDICOLEGAL ABSTRACTS

Insanity: Right of Accused to Demand Court Appointment of Psychiatrists for Use as Expert Witnesses.—The petitioner was indicted for murder and found guilty by the trial court. Successive appeals were taken to the Supreme Judicial Court of Massachusetts, the United States District Court, the United States Court of Appeals, back to the Supreme Judicial Court of Massachusetts, back to the United States District Court, and, finally for the second time, to the United States Court of Appeals, First Circuit.

The petitioner had orally and voluntarily admitted the killing and assigned counsel tried to develop a jury issue on the sanity of the accused. This being a capital case, it was mandatory under the so-called Briggs Law, Massachusetts General Law, chapter 123, section 100A, as amended by statutes 1941, chapter 194, section 11, for the clerk of the superior court to give notice to the department of mental health, which "shall cause such person to be examined with a view to determine his mental condition and the existence of any mental disease or defect which would affect his criminal responsibility." The statute directs that the report from the department of mental health be filed with the clerk of the court, where it is to be made accessible to the court, the probation officer, the district attorney, and the attorney for the accused. Pursuant to the Briggs Law, the petitioner was examined on behalf of the department of mental health by Drs. Chambers and Dexter. Their joint report, which was duly filed, found that the petitioner "is neither feebleminded nor insane, and that he does know the difference between right and wrong. . . . . This prisoner is not suffering from any mental disease or defect which would affect his criminal responsibility."

The defense counsel, said the court, could have called Dr. Chambers and Dr. Dexter as witnesses, but in view of the conclusions reached in their report counsel naturally wanted to seek out other experts whose opinion, after psychiatric examination, might be more favorable to the defense of insanity. Under Massachusetts law "reasonable expenses incurred and paid by counsel assigned by the court for the defense of a person indicted for murder, who is otherwise unable to procure counsel, shall be paid by the county where the indictment is found after approval by a justice sitting at the trial or other proceedings of the case." Rule 96 of the superior court rules further provided: "The court will not allow compensation for the services of an expert or expert witness for the defense in a capital case unless an order of the court or a justice, naming such expert or expert witness and authorizing his employment, was made before he was employed." The counsel for the accused filed a motion in the superior court asking that the defendant, being without funds, "be allowed to employ two psychiatrists at the expense of the Commonwealth so that he may properly defend himself against the crime as charged by the Commonwealth." It was this point that was appealed to the various courts and finally to the court of appeals rendering the present decision.

It had been the petitioner's contention that if he were denied, because of his lack of funds, the right to employ medical experts at the expense of the state, such denial was a violation of his constitutional rights under the 14th amendment. "While we do not think that the petitioner's constitutional argument may fairly be characterized as frivolous," said the court of appeals, "we have reached the conclusion after careful consideration that the point is not well taken."

This is not a case in which the state has refused to provide an impartial psychiatric examination of the accused with a view to determining his sanity and criminal responsibility. Quite the contrary, in compliance with a mandatory provision of law, the state has, at public expense, provided such examination by two impartial experts, and their joint report has been made available to the defense. The physicians designated by the department of mental health to make the examination, continued the court, are not partisans of the prosecution, though their fee is paid by the state, any more than is assigned counsel for the defense beholden to the prosecution merely because he is, as here, compensated by the state. Each is given a purely professional job to do—counsel to represent the defendant to the best of his ability, the designated psychiatrists impartially to examine into and report upon the mental condition of the accused. Before the Briggs Law was passed the procedure employed in ascertaining the mental responsibility of persons accused of crime was almost inconceivably futile, cruel and wasteful, said the court. Hardly a day passed, and certainly never a week without the spectacle in some one of our courts of two or more physicians, possibly graduates of the same medical school, and belonging to the same scientific and medical societies, pitted against each other, testifying to diametrically opposed opinions as to the mental condition and responsibility of the person in question. The virtual elimination of contending medical men in criminal trials, following the application of the Briggs Law, has raised the medical profession in the opinion of the public and of the press. Instead of the common spectacle of members of the medical profession pitted against each other, we have since the law was passed in 1921 an average of less than one case a year in which psychiatrists have testified in opposition in the same criminal case. Thousands and thousands of dollars have been saved, not only to the State but to the defendants, and our mentally sick offenders, instead of being executed or punished by imprisonment and perhaps turned loose in a few years in an irresponsible condition to commit further crimes, thus becoming recidivists, are placed in hospitals where they remain, perhaps for life, unless they fully recover, and both they and the public are protected. Although the Briggs Law has been justly credited with the desirable consequence of having sharply curtailed the number of unseemly disputations between psychiatric experts in criminal trials, it is true that examination and report by the psychiatrists appointed by the department of mental health does not legally preclude the introduction of expert witnesses by the defense in contradiction of the conclusions of the report by such designated impartial psychiatrists. The petitioner's contention comes to this, said the court of appeals, that the state has the constitutional obligation to promote such a battle of experts by supplying defense counsel with funds wherewith to hunt around for other experts who may be willing, as witnesses for the defense, to offer the opinion that the accused is criminally insane. We do not think that this is so, at least in a case like the present, where there has been no challenge of the professional standing and competence of the psychiatrists whose examination and report has been furnished at state expense, and no question has been raised as to their complete impartiality or as to the thoroughness of their examination of the accused. It turned out that the report in this case by Drs. Chambers and Dexter was not useful to the defense in establishing a legal defense of insanity, because of the conclusion which these impartial psychiatrists reached. But suppose the defense motion had been granted here, and assigned counsel had been authorized to employ two other experts to examine the accused. The two so chosen might, after examination of the defendant, have arrived at the same professional conclusion stated in the report of the psychiatrists designated by the department of mental health. Would the defendant then be entitled to further financial assistance from the state to continue the search, merely because a defendant of ample private wealth would perhaps have been able eventually to find a more favorable psychiatrist somewhere in the United States or even in Europe? We would think not; examination and report by two competent and impartial experts supplied at state expense is enough, we think, to satisfy the state's constitutional obligation under the due process clause. In the absence of some authoritative precedent to the contrary, we are unwilling to say, under all the circumstances present, in this case that the trial court's denial of the defense motion violated a "principle of justice so rooted in the traditions and conscience of our people as to be ranked as fundamental."

Accordingly, the order of the district court denying the petitioner's motion for the appointment of additional psychiatrists for use as expert witnesses was upheld. *McGarty v. O'Brien, 188 F. (2d) 151 (1951).*

Evidence: Admissibility of Results of Lie-Detector and Truth Serum Tests.—The defendant was charged with the crime of rape in the first degree. From a verdict and judgment of guilty, he appealed to the criminal court of appeals of Oklahoma.

The defendant's motion for a new trial, which had been denied, related to facts surrounding both a lie-detector test and a truth serum test, the defendant contending that he should have been permitted to show the voluntary taking of both tests and that their results were negative.

The question was one of first impression so the court thoroughly reviewed the cases from other jurisdictions and articles on the subject. The theory of the lie-detector, said the court, is founded on the results of discoveries made by numerous persons over a considerable number of years that, when there is an attempt to deceive, in most instances the blood pressure of the subject increases, his pulse rate changes, his breathing is apt to be shallow and suppressed, and fluctuations occur in his electrical resistance, revealed by activity of the sweat glands. A polygraph records on a moving strip of paper, driven by a small motor, the various changes which occur while the subject is undergoing questioning. The literature seems to indicate, continued the court, that the tests have proven correct in their diagnosis in about 75% of the instances used. The factors responsible for the 25% of failures are listed as follows by Fred E. Inbau, Professor of Law, Northwestern University, in a recent work on "Lie Detection and Criminal Investigation":

"(1) Emotional tension—, 'nervousness'—experienced by a subject who is innocent and telling the truth regarding the offense in question, but who is nevertheless affected by

(*a*) fear induced by the mere fact that suspicion or accusation has been directed against him, and particularly so in instances where the subject has been extensively interrogated or perhaps physically abused by investigators prior to the time of the interview and testing by the lie-detector examiner; and

(*b*) a guilt complex involving another offense of which he is guilty.

"(2) Physiological abnormalities, such as

(*a*) excessively high or excessively low blood pressure;

(*b*) diseases of the heart;

(*c*) respiratory disorders, etc.

"(3) Mental abnormalities, such as

(*a*) feeblemindedness, as in idiots, imbeciles, and morons;

(*b*) psychoses or insanities, as in manic depressives, paranoids, schizophrenics, paretics, etc.;

(*c*) psychoneuroses, and psychopathia, as among so-called 'peculiar' or 'emotionally unstable' persons—those who are neither psychotic nor normal, and who form the borderline between these two groups.

"(4) Unresponsiveness in a lying or guilty subject, because of

(*a*) lack of fear of detection;

(*b*) apparent ability to consciously control responses by means of certain mental sets or attitudes;

(*c*) a condition of 'sub-shock' or 'adrenal exhaustion' at the time of the test;

(*d*) rationalization of the crime in advance of the test to such an extent that lying about the offense arouses little or no emotional disturbance;

(*e*) extensive interrogation prior to the test

"(5) Unobserved muscular movements which produce ambiguities or misleading indications in the blood pressure tracing." We are of the opinion, said the court, that the foregoing enumerated difficulties alone in connection with the lie-detector present obstacles to its acceptability as an instrument of evidence in the trial of criminal cases, notwithstanding its recognized utility in the field of discovery and investigation, for uncovering clues and obtaining confessions. This conclusion is in line with the weight of authority repudiating the lie-detector as an instrument of evidence in the trial of criminal cases. In addition, the authorities give other cogent reasons for its inadaptability as an instrument of evidence in the trial of cases such as the impossibility of cross-examining the machine (a constitutional impedient) and those human elements of fallability which surround interpretation of the lie-detector recordings. In this connection, these devices are unlike the science of handwriting, or fingerprinting and x-ray, which reflect demonstrable physical facts that require no complicated interpretation predicated upon the hazards of unknown individual emotional differences, which may and oftentimes do result in erroneous conclusions. The use of the lie-detector would resolve into a swearing match, said the court, and, not to overlook the human elements, we can foresee conditions where to ascertain the truth, it would become necessary to require the operator of the machine to submit to a test to determine the truthfulness of his interpretations. The logic and reason set forth in the cases which have considered this subject, the court concluded, make our conclusions herein escapable. It was not error for the trial court to sustain objection to the defendant's attempt to prove the fact of taking and the results of the lie-detector test.

As to the truth serum test, it is even more experimental than the lie-detector test, said the court. The term truth serum like "lie-detector" is a misnomer. There is no specific serum which will cure or reveal deception—no drug which will infallibly induce truth. There are however, certain drugs which deeply affect one's consciousness. In such a mental state, the subject is not in a position where he can readily determine the type of answers to give to questions put to him. His ability to associate thoughts and express only those which he wishes others to hear is diminished, and as a result it is exceedingly difficult for the subject to attempt deception. Thus narcoanalysis or narcosynthesis does not describe the use and effect of a truth serum, but rather the process of inducing a state of mind by the application of a drug whereby an individual's capacity to unite thoughts and choose those to which he desires to give utterance is inhibited. It is therefore apparent, concluded the court, that the efficacy of neither the lie-detector nor the truth serum test have gained that standing and scientific recognition or demonstrated that degree of dependability necessary to justify the courts in approving their use in the trial of criminal cases. The trial court was not in error in sustaining the state's objection to the defendant's tender of the results of such test to which he contends he consented.

Accordingly the judgment of guilty was affirmed.—*Henderson v. State, 230 P. (2d) 495 (Oklahoma, 1951).*

MEDICAL MOTION PICTURES

Urinary Infections: Bacteriology, Pathology, Treatment. 16 mm. color, sound, showing time 45 minutes. Produced in 1951 under a grant for postgraduate instruction for the Nepera Chemical Co., Inc., by Medical Film Guild, New York. Directed by Dr. Grayson Carroll, St. Louis University, in collaboration with Dr. Victor F. Marshall, Cornell University Medical College. Procurable on loan from Medical Film Guild, Ltd., 167 West 57th St., New York 19.

This is a textbook type of film that deals with basic material in the etiology, diagnosis, and treatment of urinary infections. The film begins with the historical background of urine examination and the early history of the cystoscope. The hematogenous, urogenous, and lymphogenous routes of infection are depicted, and foci of infection and urinary tract obstructions are analyzed both radiographically and clinically. Methods for laboratory examination of the nine most important infecting organisms are analyzed to establish a coordinated regimen of treatment.

Four major photographic approaches are used. They include clinical cases ranging from simple obstructions of the urethra to complicated infections of the genitourinary system; animated models and animated diagrams depicting sources of obstruction in the kidney, ureters, and bladder; freshly extirpated specimens coordinated with their x-rays; and charts. A bacteriological assay is made of the nine major infecting organisms, and a series of biochemical studies show the six testing methods used for isolating an organism. In vivo and in vitro studies illustrate methods of inhibiting the organism.

The length and comprehensiveness of this film make it necessary that it be viewed several times if it is to be completely understood. For the same reason it would be advisable to have an accompanying brochure in which all of the many statistics given in the film would be repeated. This picture would provide the intern who is to begin urological service with good review material and is of possible interest to the general practitioner who is interested in a review of the subject. The photography and narration are good.

MEDICAL LITERATURE ABSTRACTS

UNITED STATES

A.M.A. Arch. Neurology and Psychiatry, Chicago

66:119-252 (Aug.) 1951

*Exfoliative-Cell Diagnosis of Central Nervous System Lesions. W. R. Platt.—p. 119.
Malignant Tumors in Institutionalized Psychotic Population. A. E. Scheflen.—p. 145.
Use of Methylphenylsuccinimide in Treatment of Petit Mal Epilepsy. F. T. Zimmerman.—p. 156.
*Effects of Administration of Adrenocorticotropic Hormone (ACTH) on Patients with Myasthenia Gravis. C. Torda and H. G. Wolff.—p. 163.
Tumors of Spinal Cord Associated with Choking of Optic Disks. J. G. Love, H. P. Wagener and H. W. Woltman.—p. 171.
Clinical and Pathological Findings in Case of Dystrophia Myotonica. W. A. Den Hartog Jager.—p. 178.
*Lesions of Transorbital Lobotomy. W. Freeman and J. M. Williams. —p. 191.
Pneumoencephalographic Study of Cerebrospinal-Fluid Absorptive-Block Mechanisms: Study of Mechanism Involved in Production of Increased Intracranial Pressure. R. B. Aird and D. Zealear.—p. 199.

Exfoliative-Cell Diagnosis of Nerve Lesions.—In the differential diagnosis of a suspected cerebral space-occupying mass, needle aspiration of the involved region is often employed to ascertain whether the mass is a tumor, localized inflammatory process, hemorrhagic process, cystic neoplasm, or a degenerative or parasitic process. In this investigation the Papanicolaou technique was applied to the fluids obtained. A study was first made of the cellular components of relatively normal fluids from the lateral ventricles, cisterna magna, and spinal canal. Of 12 cases reported on, four showed normal cytological characteristics. Three were cases of cerebral neoplasm in which it was possible to demonstrate exfoliated malignant cells in the lateral ventricle, the cisterna cerebellomedullaris, and the lumbar portion of the spinal canal. In the remaining five cases of cerebral cysts desquamated malignant cells could be demonstrated. The Papanicolaou cytological technique was used as an adjunct to other clinical, roentgenologic, and laboratory findings, in the differentiation of neoplasms from congenital, degenerative, and inflammatory states. The presence of mononuclear type cells other than lymphocytes in ventricular, cisternal, spinal, and cerebral cyst fluids should arouse suspicion of an exfoliating tumor somewhere in the axis of the central nervous system. The method does not supplant any neurological procedure in the diagnosis and localization of lesions of the central nervous system and is not intended to be a specific, final diagnostic criterion on which any operative procedure is based.

Corticotropin in Myasthenia Gravis.—Fifteen patients between the ages of 18 and 61 with myasthenia gravis of from one to 17 years' duration were treated with corticotropin (ACTH). Each patient received 25 mg. of the drug every six hours for five days. After administration of corticotropin, the intake of neostigmine bromide, as well as of other drugs, was regulated according to the needs of the patient. Electromyographic records were made, and the ability of serum to support acetylcholine synthesis was tested before, during, and after administration of corticotropin. A significant partial remission of long duration was induced by the drug in 10 of the 15 patients. Occurrence of remission could not be definitely established in four patients who were mildly ill with myasthenia gravis. During the last two days of administration of corticotropin and for a few days thereafter, disability gradually increased, consisting mainly of asthenia, malaise, headache, insomnia, and, in some instances, dyspnea. One patient with "bulbar" manifestation died on the third day of administration of corticotropin. The severity of symptoms seemed to be reduced by concurrent oral administration of 3 to 5 gm. of potassium chloride during administration of corticotropin and for one day thereafter. New courses of treatment with corticotropin (500 mg. per course) at intervals of 4 weeks to 10 months induced further remission in all patients. Corticotropin seemingly has a specific effect on the mechanism responsible for the symptoms of myasthenia gravis by increasing the synthesis of acetylcholine and by restoring to normal the impaired ability to maintain the amplitude of the action potential during repetitive stimulation. The effect of corticotropin on the nerve is due to an indirect mechanism involving an increase in the intracellular concentration of substances that augment the activity of choline acetylase.

Lesions of Transorbital Lobotomy.—Necropsy performed on 15 patients at various periods up to one year after transorbital lobotomy revealed that this rather new and relatively safe procedure produces minor lesions of the skull and dura. The distinctive lesions are within the white matter, the incision severing the thalamofrontal radiation just lateral to the anterior horn of the lateral ventricle and sometimes penetrating the ventricle and lacerating the caudate nucleus. There is sometimes a hemorrhagic cavity in the frontal white matter, which evolves into a cyst with pigmented walls. Wallerian degeneration can be traced into the frontal lobe and also through the internal capsule into the pons. Retrograde degeneration of the thalamus is milder than that seen after prefrontal lobotomy. From the pathological standpoint, transorbital lobotomy is a clean-cut, selective operation for severing the thalamofrontal radiation.

American Heart Journal, St. Louis

42:161-320 (Aug.) 1951

*Heart in Acute Hemorrhage: Clinical and Electrocardiographic Study. S. Dack, E. Corday and A. M. Master.—p. 161.
Bizarre Pulmonary Roentgenographic Manifestations in Heart Disease. W. Newman and H. G. Jacobson.—p. 184.
Thromboembolic Phenomena Associated with Rapid Diuresis in Treatment of Congestive Heart Failure. R. J. Marvel and W. A. Shullenberger. —p. 194.
Experimental Parasystole. D. Scherf and F. B. Chick.—p. 212.
Correlation of Electrocardiographic Pattern of Right Heart Strain and Evidence of Right Ventricular Hypertension in Congenital Heart Disease. A. Gordon and H. Goldberg.—p. 226.
Spatial Vectorcardiography: Normal Vectorcardiogram. VI. L. Scherlis, R. P. Lasser and A. Grishman.—p. 235.
Effect of Certain Hormones and Miscellaneous Compounds on Serum Disease in Rabbit. W. M. Govier and E. S. Feenstra.—p. 266.
Effect of Rutin in Experimental Malignant Hypertension. H. K. Hellerstein, J. L. Orbison, S. Rodbard and others.—p. 271.
*Termination of Auricular Fibrillation in Dogs with Procaine Amide Hydrochloride. M. Schlachman, J. W. Benjamin and R. Terranova. —p. 284.
Studies with Gitalin (Amorphous) for Treatment of Patients with Congestive Heart Failure. R. C. Batterman, A. C. DeGraff, L. B. Gutner and others.—p. 292.
Use of Dramamine in Vestibular Disturbances Complicating Hypertensive and Arteriosclerotic Heart Disease. I. R. Goldman, N. S. Stern and T. N. Stern.—p. 302.
Altered Metabolic Response Prior to Development of Hypertensive Vascular Disease. G. A. Perera.—p. 308.

Heart in Acute Hemorrhage.—Clinical and electrocardiographic manifestations of coronary insufficiency and the factors responsible for its production were studied in 21 men and 7 women with acute hemorrhage. One-half of the patients were over 50. The site of the hemorrhage was the gastrointestinal tract in 25, the nose and mouth in 2 with myelogenous leukemia, and the bronchi in 1 with mediastinal neoplasm. All patients were given blood transfusions early, receiving an average of 1,650 cc. of whole blood. Significant electrocardiographic changes, consisting of depression of the RS-T segment and partial or complete inversion of the T wave, were observed during the acute stage of the hemorrhage in 24 of the 28 patients. These

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An asterisk (*) before a title indicates that the article is abstracted.

changes usually progressed during the first three or four days after admission to the hospital and then began to regress gradually, lasting from 3 hours to 30 days. In 8 of these 24 patients there was lowering or inversion of the T wave after the electrocardiogram had returned to normal. These transient changes, which lasted from 2 to 13 days, started on the 6th day in three patients, on the 10th day in two patients, on the 12th day in three patients, and on the 13th day in a patient who had not shown any changes during the acute phase. In two patients with massive gastrointestinal hemorrhage, deep Q waves and slightly elevated RS-T segments appeared in the precordial leads on the second day after admission, resembling the pattern of myocardial infarction due to acute coronary occlusion. In the older patients, particularly those with antecedent coronary sclerosis or hypertensive heart disease, the electrocardiographic changes were more pronounced and followed lesser degrees of hemorrhage than in the younger patients. Precordial or substernal pain was experienced by eight patients during acute hemorrhage, and five had signs of congestive heart failure. The authors believe that the electrocardiographic changes following hemorrhage are due to an intrinsic change in the myocardium as a result of myocardial ischemia and anoxia. The factors possibly responsible for the coronary insufficiency and myocardial anoxia were shock, drop in blood pressure, tachycardia, and acute anemia. No single factor was always responsible for the acute coronary insufficiency, a combination of factors being present in each case. The most striking electrocardiographic changes did not always coincide with the maximal changes in blood pressure, heart rate, and hemoglobin, in fact, they usually followed the hemodynamic changes. A small pulmonary embolus from the deep leg veins may have been responsible for the delayed electrocardiographic changes. Clinical and electrocardiographic observations reemphasize the value of prompt treatment of hemorrhage, particularly in patients with coronary or hypertensive heart disease.

Procaine Amide Hydrochloride in Experimental Auricular Fibrillation.—Auricular fibrillation was induced in dogs by a 0.2% acetylcholine solution or by 100% tetraethylpyrophosphate, either applied topically or injected subepicardially in the region of the sinoauricular node or right auricular appendage. Simultaneously, the peripheral end of the right vagus nerve was stimulated with faradic current for a few seconds until auricular standstill occurred. When it was certain that the auricular arrhythmia was not transient, two series of experiments were done. Four dogs were given rapidly 25 to 100 mg. of procaine amide hydrochloride in a 10% solution as a single injection into the external jugular vein. In a fifth dog 0.05 cc. of a 10% solution (5 mg.) of procaine amide hydrochloride was injected subepicardially into the auricular site previously used to produce the auricular arrhythmia, and the same procedure was repeated four times. Procaine amide restored normal sinus rhythm in every case. The transition from auricular arrhythmia to normal sinus rhythm was always sudden, and once normal sinus rhythm was established it was permanent. The cessation of the rapid, irregular tachycardia by the intravenous injection of procaine amide hydrochloride took 9 to 30 seconds, and the termination of auricular fibrillation by subepicardial injection varied from 0.5 second to 26 seconds. The termination of auricular fibrillation within 0.5 second indicates that the action is not due to a metabolized product of procaine amide hydrochloride. The number of experiments as yet is too few to make a definite statement as to the smallest effective dose.

American Journal of Orthopsychiatry, New York

21:445-666 (July) 1951. **Partial Index**

Illness and Role of Physician: Sociological Perspective. T. Parsons.—p. 452.
Popular Response in Rorschach Records of Normals, Neurotics and Schizophrenics. H. B. Molish.—p. 523.
Some Contributions of Psychological Tests to Therapeutic Planning. S. Reichard.—p. 532.
Treatment of Childhood Schizophrenia in Child Guidance Clinic. A. A. Fabian and M. A. Holden.—p. 571.
Changes in Human Figure Drawings by Patients Who Recover from Regressed States. A. H. Modell.—p. 584.
Family and Staff in Hospital Psychiatric Therapy of Children. S. A. Szurek.—p. 597.
Self Re-Referral in Adolescent Girl: Workshop, 1950. W. B. Curtis and E. B. Carpon.—p. 621.

American Journal of Pathology, Ann Arbor, Mich.

27:537-760 (July-Aug.) 1951

*Effect of Cortisone on Lesions of Periarteritis Nodosa. A. H. Baggenstoss, R. M. Shick and H. F. Polley.—p. 537.
"Cardiac" or Congestive Cirrhosis of Liver. P. Kotin and E. M. Hall.—p. 561.
Primary Carcinoma of Liver in Hemochromatosis. S. Warren and W. L. Drake Jr.—p. 573.
Histochemically Demonstrable Glycogen in Human Heart: With Special Reference to Glycogen Storage Disease and Diabetes Mellitus. R. W. Mowry and R. Bangle Jr.—p. 611.
Primary Reticulo-Endothelial Granulomas: With Report of Atypical Case of Letterer-Siwe's Disease. J. W. Dennis and P. D. Rosahn.—p. 627.
Toxoplasmosis of Captive Wild Birds and Mammals. H. L. Ratcliffe and C. B. Worth.—p. 655.

Cortisone in Periarteritis Nodosa.—Two patients critically ill with periarteritis nodosa were observed for 75 and 146 days respectively. The first received 3.62 gm. and the second received 13.72 gm. of cortisone. Despite initial improvement, both died of cardiac and renal failure. Histologically, the most remarkable finding was the apparently complete healing of all arterial lesions. All histological signs of inflammation had disappeared in the first case within three weeks and in the second within three months after biopsy had disclosed acute arteritis. In the first case histological examination of multiple sections from all organs failed to reveal active inflammation in any vessel. In the process of healing, however, fibrous obliteration of the lumina of these vessels occurred and resulted in infarcts, which were particularly numerous in the kidneys, heart, and intestinal tract. The healed arterial lesions were characterized by severe intimal fibrosis, by focal defects and sometimes complete destruction of the elastic lamellae, and by fibrosis of the media, adventitia, and perivascular tissue. Vascularization of the intima and phagocytes containing hemosiderin were frequent. In the second case, the histological findings were similar, except that aneurysm, thrombosis, and hemorrhage were commoner. In both cases, histological examination of the suprarenal cortex revealed moderate atrophy and a decrease in lipoid content. Although the histological appearance of the healed lesions in these cases did not differ from the appearance of lesions observed in cases in which spontaneous healing has been described, the healing in these cases occurred more quickly than has ever been reported.

Am. J. Roentgenol. & Rad. Therapy, Springfield, Ill.

66:171-340 (Aug.) 1951

*Observations and Results in Treatment of Hyperthyroidism with Radioactive Iodine (I^{131}). W. G. Scott, W. B. Seaman, C. MacBryde and others.—p. 171.
*Experiences in Treatment of Diseases of Thyroid Gland with Radioactive Iodine. U. V. Portmann, R. A. Hays, E. P. McCullagh and C. E. Richards.—p. 179.
Carcinoma of Ovary. H. D. Kerr and H. B. Elkins.—p. 184.
Roentgenological Manifestations of Gastroduodenal Ulceration in the Newborn. L. L. Lemak.—p. 191.
Carcinoids (Argentaffinomas) of Stomach. R. H. Marshak and A. I. Friedman.—p. 200.
Roentgen Changes in Upper Intestinal Tract Following Use of Calcium Chloride in Neonatal Tetany. W. C. Hall.—p. 204.
Roentgen Demonstration of Deposition of Colloidal Thorium Dioxide (Thorotrast) in Gallbladder Wall: With Report of Case. E. L. Pirkey, R. C. Taylor, A. J. Miller and others.—p. 208.
Epiplopericolitis: Significance of Its Roentgenological Diagnosis. S. Di Rienzo and L. G. Mosca.—p. 215.
Spontaneous Pneumourography Following Ureterosigmoid Transplantation. R. E. Parks.—p. 222.
Spontaneous Pneumocephalus: Report of Case Occurring in Course of Carcinoma of Nasopharynx. L. Raider.—p. 231.
Esophagobronchial Fistula Through Esophageal Diverticulum: Report of Case with Treatment by Cauterization. D. L. Jenkinson and L. C. Bate.—p. 236.
Myelography with Skiodan. S. Arnell.—p. 241.
Effect of Antisplenic Tissue Serum on Roentgen-Ray Damage (Whole Body Irradiation). N. Molomut, M. Friedman, I. J. Ryby and A. Haber.—p. 245.
Essentials of Stereoscopic Roentgenography. L. E. Etter.—p. 248.

Radioactive Iodine in Hyperthyroidism.—Of 269 patients with hyperthyroidism treated with radioactive iodine (I^{131}), 195 were followed for six months to three years. Of the 195 patients, 117 had diffuse toxic goiter, 35 had multinodular goiter, 36 had thyrotoxicosis following subtotal thyroidectomy, and seven had thyrotoxicosis uncontrolled by roentgen therapy. Most of the

patients with diffuse goiter were given 0.2 mc. per estimated gram of thyroid tissue, but this was later reduced to 0.15 mc. Patients with nodular goiter and with recurrent hyperthyroidism following surgical or roentgen therapy were usually treated with slightly larger doses, since they seemed to be more resistant to radioactive iodine. A satisfactory remission was obtained with radioactive iodine in 80 patients with diffuse goiter, in 28 with nodular goiter, and in 22 of the patients with recurrent hyperthyroidism following surgical or roentgen therapy, i. e., in 68% of all patients. Of these, 20% now require some supplemental thyroid therapy. In the remaining 32%, evaluation has been impossible because of inadequate follow-up. The authors feel that the results have established a place for radioactive iodine in the treatment of selected cases of hyperthyroidism. The optimum dosage range appears to lie between 0.09 to 0.2 mc. per estimated gram of thyroid tissue. It is better to favor the smaller dosage and repeat once if necessary than to produce low hypothyroid states. With greater clinical experience and improvement in physical methods a more accurate determination of the optimum dose should be possible.

Radioactive Iodine in Treatment of Diseases of Thyroid Gland.—Of 281 patients with hyperthyroidism treated with radioactive iodine, 203 had diffuse toxic goiter and 78 had nodular toxic goiter. The initial dose was estimated to be the smallest necessary to produce physiological response according to the size and type of goiter. In general, 7 mc. was the initial dose for diffuse toxic goiter in patients with small thyroid glands; in some patients with unusually large thyroid glands or severe hyperthyroidism, the initial dose was 14 or 17 mc., and patients with nodular toxic goiter were given 20 or 25 mc. Of 194 patients with diffuse toxic goiter followed for three or more months, at least 60% were in remission in about four months after a total dosage averaging approximately 12 mc., regardless of basal metabolic rate or estimated weight of the goiter. Sixteen patients were not in remission when last seen; four of these still have hyperthyroidism and two have been followed for only three months. Recrudescence of hyperthyroidism developed after primary control in five patients (2.5%) and hypothyroidism in approximately 10%. Of the 78 patients with nodular toxic goiter, 18 (23%) still have hyperthyroidism requiring additional treatment. The severity of the hyperthyroidism in these patients appears to have little relation to the weight of the gland, basal metabolic rate, or the dosage of radioactive iodine required for remission. The dosage for remission is higher for nodular than for diffuse toxic goiter, and the time required for control is longer. Hypothyroidism did not develop in any of the patients with toxic nodular goiter.

American Journal of Tropical Medicine, Baltimore

31:411-534 (July) 1951. Partial Index

An Easier and More Accurate Diagnosis of Malaria and Filariasis Through Use of Skin Scarification Smear. L. van den Berghe and M. Chardome.—p. 411.
Laboratory Results on Efficacy of Terramycin, Aureomycin and Bacitracin in Treatment of Asymptomatic Amebiasis. J. E. Tobie, H. Most, L. V. Reardon and J. Bozicevich.—p. 414.
Treatment of T. Saginata and H. Nana Infestations with Atabrine. M. T. Hoekenga.—p. 420.
Comparison of Aureomycin and Carbarsone in Treatment of Intestinal Amebiasis. M. T. Hoekenga.—p. 423.
Effect of Ascorbic Acid Deficiency on Resistance of Guinea-Pigs to Infection with Endamoeba Histolytica of Human Origin. E. H. Sadun, J. L. Bradin Jr. and E. C. Faust.—p. 426.
Effect of Heat-Treatment on Respiration of Trypanosoma Cruzi Used for Cultivation of Endamoeba Histolytica. M. Nakamura and H. H. Anderson.—p. 438.
Balantidium Coli Infection with Special Reference to Treatment. H. B. Shookhoff.—p. 442.
Propagation of Japanese Encephalitis Virus in Mosquito by Parenteral Introduction and Serial Passage. H. S. Hurlbut.—p. 448.
Plague. V. B. Link.—p. 452.
Electronmicrography of Treponemas from Cases of Yaws, Pinta, and So-Called Cuban Form of Pinta. J. J. Angulo, J. H. L. Watson, C. C. Wedderburn and others.—p. 458.
Cardiac Manifestations of Weil's Disease. W. A. Sodeman and J. H. Killough.—p. 479.
Toxicity of Principal Snake Venoms of Brazil. W. H. A. Schöttler.—p. 489.

Annals of Surgery, Philadelphia

134:1-144 (July) 1951

Critical Evaluation of Subtotal Gastrectomy for Cure of Cancer of Stomach. G. McNeer, H. VanderBerg Jr., F. Y. Donn and L. Bowden.—p. 2.
Electrical Artificial Pacemaker for Standstill of Heart. J. C. Callaghan and W. G. Bigelow.—p. 8.
*Treatment of Hyperthyroidism: Evaluation of Thyroidectomy, of Prolonged Administration of Propyl Thiouracil, and of Radioactive Iodine. G. Crile Jr. and E. P. McCullagh.—p. 18.
*Significance of Nipple Discharge. W. T. Fitts Jr., J. D. Maxwell and R. C. Horn Jr.—p. 29.
*Surgical Experiences with Pheochromocytoma. V. Richards and F. N. Hatch.—p. 40.
Correction of Ankylosis of Jaw and Associated Deformities of Face. K. L. Pickrell, N. J. Wilde, B. F. Edwards and others.—p. 55.
Portal Circulation in Experimental Hemorrhagic Shock: In Vivo Roentgen Ray Studies. E. W. Friedman, H. A. Frank and J. Fine.—p. 70.
Radical Pancreaticoduodenectomy: Report of Two Autopsies Performed Five and Four Years After Operation. C. G. Child III and J. T. Ellis.—p. 80.
Congenital Abnormalities of Intestinal Rotation and Mesenteric Attachment—Cause of Intestinal Obstruction in Adult. R. B. Brown and D. Ross.—p. 88.
Choledochojejunostomy: Its Role in Treatment of Chronic Pancreatitis. R. F. Bowers and J. Greenfield.—p. 99.
Phlebography of Leg in Erect Position. H. W. Scott Jr. and J. F. Roach.—p. 104.
Stenosing Tenosynovitis at Radial Styloid Process (De Quervain's Disease). P. R. Lipscomb.—p. 110.
Defibrillation of Ventricles by Electric Shock with Complete Recovery. J. Johnson, C. K. Kirby and R. D. Dripps.—p. 116.
Interligamentous Inguinal Hernia: Classification and Statistical Study of 117 Hernias. C. C. Burton.—p. 119.
Spontaneous Rupture of Normal Kidney Parenchyma: Report of Case. G. E. Murphy and C. H. Harney.—p. 127.
Acute Perforation of Jejunum Secondary to Primary Jejunitis: Case Report. B. O. Garner, C. E. Claugus and J. E. Hamilton.—p. 131.
Bilateral Chylothorax: Unusual Complication of Radical Neck Dissection with Recovery. E. L. Frazell, C. C. Harrold Jr. and L. Rasmussen.—p. 135.
Hemangio-Endothelioma Originating in Peripheral Nerve: Report of Case. J. D. Conway and M. B. Smith.—p. 138.

Treatment of Hyperthyroidism.—Crile and McCullagh discuss the results obtained at the Cleveland Clinic in the treatment of hyperthyroidism by subtotal thyroidectomy, by prolonged treatment with propylthiouracil, methylthiouracil, or radioactive iodine. They base their evaluation of thyroidectomy on 540 cases, emphasizing that after preparation with propyl or methyl thiouracil thyroidectomy is more effective in nodular goiter with hyperthyroidism than it is for Graves' disease and that removal of almost all thyroid tissue is more satisfactory than incomplete operations. The use of propylthiouracil as definitive treatment is well justified in selected cases, and in others its use is justified as a means of preparing the patient for operation. Methylthiouracil is almost identical in efficiency. A dose of 300 to 400 mg. per day insures eventual effectiveness in nearly all patients, but as little as 150 mg. per day is sufficient in over half of the patients. An evaluation of 141 patients in whom administration of propylthiouracil was started prior to April, 1947, in an attempt to obtain cure revealed that 70 patients had long-standing remissions after withdrawal of therapy. Prolonged treatment with propylthiouracil or methylthiouracil is acceptable in young patients with small diffuse goiters to induce permanent remission and can also be used as an alternative to radioactive iodine in aged or debilitated patients regardless of type of goiter. From 1947 to 1950, radioactive iodine was given to 337 patients with hyperthyroidism, including 73 patients with Graves' disease who were followed from two months to two years after completion of therapy. Hyperthyroidism was completely controlled in an average of three months after the first treatment. The average total dose was 14 mc. It appears that radioactive iodine is the preferred treatment for older patients with Graves' disease, for patients with recurrent hyperthyroidism, for elderly patients with nodular goiter with hyperthyroidism, and for a selected group of younger patients with Graves' disease.

Significance of Nipple Discharge.—There is no agreement on the treatment of patients with nipple discharge. Two years ago, in studying a small series of breast lesions Fitts and co-workers noted that a solitary intraductal papilloma was rarely the cause

of a bloody discharge from the nipple; the majority of discharges were associated with multiple gross or microscopic papillomas (papillomatosis) or with other lesions, both benign and malignant. To secure further information about the disputed problem of nipple discharge they reviewed all breast lesions removed from 1942 to 1948 at the Hospital of the University of Pennsylvania and studied in its laboratory. Of 1,048 specimens, 97 (9.3%) had been associated with nipple discharge. The hospital records of these patients and the pathological specimens were analyzed in detail. The primary lesion in nearly half the cases was intraductal papillomatosis, with or without other changes of chronic cystic mastitis. Solitary intraductal papillomas, without additional gross or microscopic tumors, were encountered only five times in this series. Carcinoma was the primary disease in one-fourth and was usually wholly or largely intraductal; chronic cystic mastitis without significant intraductal papillary proliferation was noted in 9%, and a variety of inflammatory lesions dependent on ductal stasis and distention comprised 13%. The type of discharge, in particular whether it was bloody, was not a reliable diagnostic aid. In a majority of cases with nipple discharge, the source of the discharge could be localized to a single duct or duct system. Resection of the segment of the breast drained by the offending duct or duct system constitutes adequate treatment. This is the minimum operative procedure. Because of the 25% incidence of carcinoma, the authors believe that all nipple discharges should be thoroughly investigated both surgically and pathologically.

Surgical Experiences with Pheochromocytoma.—Five patients with pheochromocytoma are reported on. In the first, hypertension began with pregnancy and persisted after its termination. Splanchnic section was done bilaterally, but the adrenal glands were not explored. After this the authors carried out routine exploration of the adrenals in all sympathectomies. The relationship of pregnancy to the hypertensive state was noted also in the second case. In the third case the diagnosis was made on the classic diagnostic picture of paroxysmal hypertension. All the special diagnostic studies except the piperoxan ("benzodioxan") test, which was not then available, were normal. An alarming reaction that today might be controlled by the use of piperoxan occurred on manipulation of the tumor. The benign postoperative course without specific adrenal therapy was gratifying. In the fourth case death resulted from acute adrenal insufficiency. The fifth patient underwent cervical laminectomy for removal of an extramedullary cord tumor. Frozen sections revealed pheochromocytoma thought to be metastatic. Later an ovoid nodular pheochromocytoma was removed from the right adrenal area. Piperoxan was useful in establishing the diagnosis of pheochromocytoma and also proved of value in controlling the paroxysms of hypertension during the surgical manipulation of the tumor. The postoperative course was uneventful. According to the literature, chromaffin cell tumors arising outside the adrenal medulla (paragangliomas) occur only one-tenth as often as those arising in the adrenal (pheochromocytomas). The classic clinical picture is that of paroxysmal hypertension, but the disease should be suspected in all cases of sustained hypertension, atypical hyperthyroidism with hypertension, hypermetabolism, and mild diabetes, and in cases of sudden collapse or heart failure in young persons after minor trauma or surgical procedures. The diagnosis can be confirmed by roentgenographic studies of the adrenal areas and by the drop in blood pressure after the intravenous administration of one of the newer drugs capable of adrenergic blockade such as piperoxan. Death can occur from epinephrine intoxication during manipulation of the tumor. Piperoxan or other adrenolytic drugs may control this complication. Death in the immediate postoperative period is probably due to acute adrenal medullary and cortical insufficiency. To avoid such fatalities the patient should be given whole adrenal extract preoperatively and postoperatively whole adrenal extract, lipoadrenal extract, desoxycorticosterone, phenylephrine (neo-synephrine®) hydrochloride or norepinephrine, and blood and plasma should be utilized.

Arizona Medicine, Phoenix

8:1-88 (July) 1951

*Delays in Diagnosis of Tuberculosis from Incautious Use of Antibiotics. W. H. Oatway Jr.—p. 25.
Treatment of Common Urinary Tract Infections. R. H. Cummings.—p. 28.
Surgical Jaundice. W. H. Cleveland.—p. 33.

Use of Antibiotics Delaying Diagnosis of Tuberculosis.—In a sanatorium of 50 beds, Oatway found 20 patients in whom the diagnosis of tuberculosis had been considerably delayed because they had been treated with antibiotics, chiefly penicillin, or sulfonamides without having had roentgenologic and bacteriologic examinations. The newer antibiotics give a false sense of security because of their wide therapeutic spectrum. They must be aimed more precisely at specific infections. The physician and patient both may be responsible for the delay in diagnosis. Persons who have had tuberculosis are especially at fault if they do not inquire into the cause of pulmonary symptoms. A chest x-ray survey has been valuable in establishing a correct diagnosis in some of the cases presented in this report. Physicians should make use of the case-finding facilities.

Cincinnati Journal of Medicine

32:253-284 (July) 1951

Renal Functions in Clinical Renal Disease. A. C. Corcoran.—p. 253.

32:285-320 (Aug.) 1951

Treatment of Blast and Burn Casualties in Atomic Warfare. V. E. Siler.—p. 285.
Antabuse in Therapy of Chronic Alcoholism. G. L. Usdin.—p. 28.

Connecticut State Medical Journal, Hartford

15:567-660 (July) 1951

Statistical Study of Premature Infant. M. Bogin and K. J. Edgar.—p. 569.
Oral Cholecystogram. R. T. Ogden.—p. 573.
Further Observations on Relation of Blood Depletion to Wound Healing, with Special Reference to Suprapubic Prostatectomy. H. A. Levin.—p. 575.
Patent Omphalomesenteric (Vitelline) Duct: Case Report. L. W. Minor.—p. 578.
Treatment of Lung Abscess. D. R. Morrison.—p. 581.
State Psychiatric Hospital and Community. W. B. Terhune.—p. 584.

Gastroenterology, Baltimore

18:339-502 (July) 1951

Influence of Emotional Factors on Clinical Course of Ulcerative Colitis in Children. D. G. Prugh.—p. 339.
Effects of Age and Bed Rest on Plasma Fat Particles as Measured by Fat Tolerance Test. S. G. White, W. C. Ralston and H. O. Carne.—p. 355.
Aneurysm of Abdominal Aorta with Report of Four Unusual Cases. B. I. Hirschowitz and L. Bagg.—p. 361.
Study of Changes in pH of Gastric Contents in Peptic Ulcer Using 24 Hour Test Meal. G. Watkinson.—p. 377.
Clinical Response of Patients with Peptic Ulcer to Topical Mucigogue (Eugenol). J. Bandes, N. A. Samuels, F. Hollander and others.—p. 391.
Gastroscopy: Five Year Study in Large General Hospital. D. Niemetz, G. K. Wharton and I. H. Wilson.—p. 400.
Studies on Cephalic Phase of Gastric Secretion in Normal Subjects and Ulcer Patients. O. Noring.—p. 413.
Eosinophile Responses to Epinephrine and ACTH in Peptic Ulcer. F. P. Turner.—p. 419.
Studies on Pepsin Secretion: I. Nocturnal and Hypoglycemic Secretion in Patients With Duodenal Ulcer and Without Gastro-Intestinal Disease. A. B. Chinn, D. T. Book and A. J. Beams.—p. 427.
*ACTH Therapy for Ulcerative Colitis Complicated by Perforation of Coexisting Peptic Ulcer. S. Sloan, J. D. Briggs and J. A. Halstead.—p. 438.

Perforation of Peptic Ulcer During ACTH Therapy.—A man of 42 with a history of duodenal ulcer was treated with corticotropin (ACTH) because of symptoms of ulcerative colitis. On the eighth day of his second course of treatment he complained of dull epigastric distress and vague generalized "gas pains," slightly relieved by food. At 3 a. m. the following morning persistent abdominal pain developed, which became localized in the upper midabdomen. Despite continuous gastric suction the distention and pain increased, so that abdominal exploration was carried out 18 hours after the onset of definite pain. The

preoperative diagnosis was appendicitis, and the appendix was removed, but it was obviously not the cause of the symptoms. Accordingly, an incision was made in the right upper quadrant, and a small anterior duodenal ulcer perforation was found, with a moderate amount of fibrin sealing the opening. There was local peritonitis. The perforation was closed, and the patient had an uneventful postoperative course. The usual signs of perforated ulcer were absent in this patient. The masking of signs and symptoms of complicating infection in patients receiving corticotropin and cortisone may be misleading. This fact has also been reported in other similar case reports. This case and other recent reports suggest that corticotropin and cortisone may be detrimental to the healing of peptic ulcer. Corticotropin should be used with caution or not at all in patients who have or have had a peptic ulcer.

Georgia Medical Association Journal, Atlanta

7:279-322 (July) 1951

Fat Metabolism and Arteriosclerosis. C. F. Wilkinson Jr.—p. 279.
Diabetes Detection in Georgia. C. J. McLoughlin, L. M. Petrie and R. H. Fetz.—p. 285.
Medical Care of Service Connected Diabetes in Georgia. A. P. McGinty. —p. 287.
Male Pseudohermaphrodism. T. R. Freeman.—p. 289.
Management of Unusual Case of Anuria. R. Banks Jr. and J. P. Hill Jr. —p. 291.
Modern Treatment of Urinary Infections. H. P. McDonald, W. E. Upchurch and C. E. Sturdevant.—p. 294.
*Use of ACTH and Cortisone in Treatment of Anorexia Nervosa. R. B. Greenblatt, W. E. Barfield and S. L. Clark.—p. 299.

Corticotropin and Cortisone in Anorexia Nervosa.—The similarity between anorexia nervosa and Simmonds' disease frequently makes it difficult to differentiate them. Simmonds' disease is primarily a panhypopituitarism resulting in arrest in sexual development, amenorrhea or hypogonadal function, hypothyroidism, and adrenal cortical insufficiency. Anorexia nervosa is primarily a psychiatric disorder with onset following some emotional crisis, and the resulting polyglandular endocrine deficiency is secondary, perhaps, to a hypothalamico-pituitary "block," or to starvation. This paper presents observations on five patients with Simmonds' disease who were treated with corticotropin (ACTH) and/or cortisone. One of the five patients derived no benefit from therapy with either corticotropin or cortisone. Two of the three patients who received corticotropin responded immediately with increased well-being, strength, weight gain, and reversal of attitude. One patient who had improved as a result of corticotropin therapy derived no benefit from two subsequent courses of therapy with cortisone; however, two other patients who received cortisone alone were greatly benefited. Although edema was observed in all five cases during therapy with cortisone or corticotropin, it was controlled by oral administration of potassium chloride. Mental depression was experienced by one patient during therapy with cortisone. Insomnia and nocturnal restlessness were reported by two of three patients who received corticotropin. The authors conclude that corticotropin and cortisone are valuable adjuncts to endocrine replacement therapy for maintenance of metabolic balance in the patient with anorexia nervosa until satisfactory psychiatric readjustment is accomplished.

Indiana State Medical Assn. Journal, Indianapolis

44:433-540 (June) 1951. **Partial Index**

National Survival Under Atomic Attack. E. V. Hahn.—p. 455.
Associated Services Division. O. W. Sicks.—p. 457.
Public Health Division of Medical Services. G. F. Kempf.—p. 458.

44:541-732 (July) 1951. **Partial Index**

Individuals and Groups in Medical Practice. A. Stump.—p. 573.
Adequate Insurance Against Liability for Malpractice. A. Stump.—p. 577.
Safe Birth and Well-Being of Children Born Out of Wedlock. R. E. Jewett.—p. 580.
Historical View of Mental Hygiene Movement in Indiana. W. W. Argow and M. French.—p. 693.
Compulsory Health Insurance or Socialized Medicine. A. M. Emhardt. —p. 697.

Proc. Soc. Exper. Biol. & Med., Utica, N. Y.

77:379-588 (July) 1951. **Partial Index**

Effect of Excluding Pancreatic Juice from Duodenum on Secretory Responses of Pancreas to a Meal. D. Annis and G. A. Hallenbeck. —p. 383.
Encephalitis in the Midwest: IV. Western Equine Encephalomyelitis Virus Recovered from Nestling Wild Birds in Nature. C. A. Sooter, B. F. Howitt, R. Gorrie and T. A. Cockburn.—p. 393.
Recovery of Virus of Eastern Encephalomyelitis from Mosquito, Culiseta Melanura (Coquillett). R. W. Chamberlain, H. Rubin, R. E. Kissling and M. E. Eidson.—p. 396.
New Human Blood Factor of Rare Incidence in General Population. P. Levine, A. H. Stock, A. B. Kuhmichel and N. Bronikovsky.—p. 402.
Methods for Local Induction and Quantitative Analysis of Human Sweat. V. P. Dole, B. G. Stall and I. L. Schwartz.—p. 412.
Effectiveness of Thiocyanate Analog of Vitamin B_{12} in Pernicious Anemia. G. W. James III and L. D. Abbott Jr.—p. 416.
Effect of Nitro-Compounds and Aldehyde Semicarbazones on Virus of Primary Atypical Pneumonia. M. D. Eaton, M. E. Perry and I. M. Gocke.—p. 422.
Effect of Aureomycin on Liver Fat and Liver Function. D. A. Sutherland, J. D. Mann, B. Giges and D. Seligson.—p. 458.
Effect of Oral Thiamine Administration on Thiamine Content of Stool. J. E. Kirk and M. Chieffi.—p. 464.
Relative Role of Milk Agent and Tissue Sensitivity in Estrogen-Induced Mammary Growth. R. Silberberg, M. Silberberg and J. J. Bittner. —p. 473.
*Effect of Pertussis, Diphtheria Toxoid and Salmonella Immunization on Experimental Poliomyelitis. A. Milzer, M. A. Weiss and K. Vanderboom.—p. 485.
Effect of ACTH on Whole Blood Coagulability. J. L. Fahey.—p. 491.
Specific Soluble Substance Involved in Nephrotoxic Nephritis. L. R. Cole, W. J. Cromartie and D. W. Watson.—p. 498.
Rapid Method for Clinical Total Blood Volume Determination Using Radioactive Iodinated Human Serum Albumin (RIHSA). J. B. Aust, S. N. Chou, J. F. Marvin and others.—p. 514.
Circulating Antibodies in Vitamin-Deficiency States: Pteroylglutamic Acid, Niacin-Tryptophan, Vitamin B_{12}, A, and D Deficiencies. P. P. Ludovici and A. E. Axelrod.—p. 526.
*Experimental Production of Post-Tonsillectomy Bulbar Poliomyelitis. H. K. Faber, R. C. McNaught, R. J. Silverberg and L. Dong.—p. 532.
Effect of Therapeutic Doses of Ephedrine on Renal Clearances in Normal Man. M. H. Maxwell, P. Morales and C. H. Crowder Jr.—p. 539.
Serum Sodium Values in Essential Hypertension. H. L. Holley, H. C. Elliott Jr. and C. M. Holland Jr.—p. 561.

Effect of Immunization on Experimental Poliomyelitis.—Recent clinical evidence in Australia and England suggests that pertussis vaccine given alone or in combination with diphtheria toxoid during the poliomyelitis season results in a significantly increased frequency and clinical severity of paralysis in the inoculated limb. Milzer and associates found that Swiss mice infected intracerebrally with the Lansing strain of poliomyelitis virus show a significantly decreased incubation period before onset of paralysis following intraperitoneal inoculation with pertussis vaccine, pertussis-diphtheria toxoid, or diphtheria toxoid alone. Results were based on a series of 20 experiments carried out by two technicians working independently and involving over 650 mice. Similar results were obtained in six of seven other experiments in which infected mice were injected intravenously with Salmonella typhimurium vaccine. In an addendum to this report the authors say that they found that 30,000 units of procaine penicillin G in peanut oil given intraperitoneally at the same intervals as the pertussis vaccine had no significant effect on the incubation period before onset of paralysis.

Post-Tonsillectomy Bulbar Poliomyelitis.—Studies described in this report are summarized as follows: 1. Application of poliomyelitis virus to the pharynx of cynomolgus monkeys, followed by enucleation of the tonsils, was regularly followed after 7 to 10 days by primary bulbar paralysis, accompanied sometimes by high spinal paralysis. This effect was probably due to introduction of virus into the nerves of the peritonsillar tissues. 2. Intrathalamic inoculation of virus followed three days later by tonsillectomy was regularly followed within two more days by bulbospinal paralysis in which all levels of the cord were involved. This effect probably indicates that trauma increases the vulnerability of nerve cells to infection already present in the central nervous system. 3. After oropharyngeal swabbing with virus and without tonsillectomy, spinal paralysis usually resulted, with bulbar manifestations in only one instance. 4. With pharyngeal application of virus followed by application of 2% tincture of iodine and then by tonsillectomy, all six animals remained well.

Proc. Staff Meet. Mayo Clinic, Rochester, Minn.

26:257-272 (July 4) 1951. Partial Index

*Variable Effects of Identical Amounts of Dicumarol on Prothrombin Values of Different Persons. W. E. Wellman and E. V. Allen.—p. 257.
Use of Antacids to Control Nausea and Vomiting Caused by Terramycin. W. B. Parsons Jr. and W. E. Wellman.—p. 260.
*Mortality and Morbidity After Transurethral Resection in Cases of Parkinson's Syndrome. J. R. Longley and E. N. Cook.—p. 264.
Clinically Indeterminate Pulmonary Fibrosis: Pathologic Study. H. D. Peabody Jr., H. J. Moersch and J. E. Edwards.—p. 266.

Variable Effects of Identical Amounts of Dicumarol.®—Consecutive records were studied of 100 patients who received bishydroxycoumarin (dicumarol®), 300 mg. the first day and 200 mg. the second day, either for the treatment or for the prevention of intravascular thrombosis. The prothrombin times of the patients were widely divergent. In two instances it was not influenced; in other instances it was prolonged to 80 seconds or more. In an additional study the authors administered 300 mg. of bishydroxycoumarin on the first day. Here again the prothrombin values varied widely. This study emphasizes that there is no constantly correct dosage of bishydroxycoumarin and that treatment with this drug can be safe and efficient only when the prothrombin time is determined repeatedly at short intervals.

Prostatic Resections in Patients with Parkinson's Syndrome.—A review of 93 consecutive cases of transurethral prostatic resections in patients with Parkinson's syndrome revealed that only one death occurred in this group. The mortality rate in these patients compared favorably with that of all patients, approximately 12,500, who underwent resection during the same 10 year period.

Public Health Reports, Washington, D. C.

66:911-950 (July 20) 1951. Partial Index

Problems of Alaskan Eskimos, Indians, Aleuts. J. C. Haldeman.—p. 912.
Control of Alaskan Biting Insects. C. S. Wilson.—p. 917.
Sewage and Waste Disposal Problems. E. K. Day.—p. 922.
Biotic Interrelationships of Helminth Parasitism. R. Rausch.—p. 928.
Phlyctenular Keratoconjunctivitis Among Alaskan Indians and Eskimos. M. H. Fritz and P. Thygeson.—p. 934.

66:951-986 (July 27) 1951

Membrane Filter in Sanitary Bacteriology. H. F. Clark, E. E. Geldreich, H. L. Jeter and P. W. Kabler.—p. 951.

Surgery, St. Louis

30:1-274 (July) 1951. Partial Index

Society of University Surgeons: Essay on Medical Relations. J. M. Stevenson.—p. 1.
Sterilization of Frozen Arterial Grafts by High-Voltage Cathode-Ray Irradiation. I. A. Meeker Jr. and R. E. Gross.—p. 19.
*Surgical Treatment of Cardiac Valvular Stenosis. W. H. Muller Jr. and W. P. Longmire Jr.—p. 29.
*Use of Enzymatic Agents in Débridement of Burn and Wound Sloughs. J. F. Connell Jr. and L. M. Rousselot.—p. 43.
Observations on Circulatory Effects of Short Duration Positive Pressure Pulmonary Inflation. G. Taylor and F. Gerbode.—p. 56.
Role of Pelvic Evisceration in Surgery. E. M. Bricker and J. Modlin. —p. 76.
Radioactive Cobalt as Adjunct to Cancer Surgery. A. G. James, R. D. Williams and J. L. Morton.—p. 95.
Critique of Anterior Resection in Treatment of Cancer of Rectum and Pelvic Colon. J. E. Dunphy and E. G. Broderick.—p. 106.
Surgical Therapy for Chronic Pancreatitis. R. F. Bowers.—p. 116.
Clinical Study of Effect of Vagotomy on Recurrent Acute Pancreatitis. R. S. McCleery, J. E. Kesterson and W. R. Schaffarzick.—p. 130.
Prevention of Dilatation in Autogenous Venous and Pericardial Grafts in Thoracic Aorta: Experimental Study. Y. Sako.—p. 148.
Treatment of Hemorrhagic Shock with Cortisone and Vitamin B_{12}. J. M. Howard and M. E. DeBakey.—p. 161.
Closure of Abdominal Incision: Comparison of Mass Closure with Wire and Layer Closure with Silk. S. O. Hoerr, R. Allen and K. Allen. —p. 166.
Small Bowel Obstruction Following Combined Abdominoperineal Resection of Rectum. H. Ulfelder and W. C. Quinby Jr.—p. 174.
Pectus Excavatum and Heart Failure. M. K. Ravitch.—p. 178.
Nature of Toxic Material in Closed Loop Intestinal Obstruction: Identification of Lysozyme. R. A. Light.—p. 195.

Surgical Treatment of Cardiac Valvular Stenosis.—The authors report experiences in the treatment of pure pulmonary stenosis and of mitral stenosis. Five patients with pure pulmonary stenosis were successfully operated on by a procedure incorporating the principles of the Brock method. An adjustable valvulotome with three cutting blades was used satisfactorily in the last two patients; dilatation of the incised valve was accomplished with an expansible dilating instrument. Fourteen patients were operated on for mitral stenosis by Bailey's technique of commissurotomy. Eleven of these patients survived. A modification of Bailey's valvulotome is described. It has a hooked knife on either side and obviates the need for a second glove.

Enzymatic Agents in Débridement.—Numerous proteolytic enzymes have been developed and employed in the débridement of wounds. This paper presents clinical observations on the proteolytic activity of the streptococcic enzymes streptokinase and streptodornase. Patients with two or more lesions were studied, so that one lesion could serve as a control. So far, 12 burns and 21 wounds have been studied. Case histories are presented to demonstrate the efficacy of enzymes in burns, in postoperative wound infections, in ulcerations, and in large abscess cavities. Streptokinase and streptodornase have proved to be effective in the lysing of susceptible portions of wound exudates and sloughs, but, to aid in the atraumatic separation of slough, they must have the proper substrates as part of the slough-tissue separation reaction. The studies made it apparent that many different substrates go into the make-up of various sloughs and these substrates will require the proper proteolytic enzyme system for lysis. In burn and wound sloughs it was necessary to cross-hatch the slough into 3 by 5 mm. squares for the enzymes to reach their specific substrates. Collagenous material, epithelial cells, and fibroblastic cells are not in the spectra of the proteolytic activity of streptokinase and streptodornase. The enzymes must be replenished at least every 24 hours, or earlier, depending on the amount of concomitant exudate-transudate elaborated by the lesion. Local use of antibiotics may be justified as the dead tissue foci are removed. No serious local or systemic toxic manifestations were noted.

Tennessee State Medical Assn. Journal, Nashville

44:271-320 (July) 1951

SYMPOSIUM ON ACTH AND CORTISONE

Introduction. C. J. Deere.—p. 271.
Experiences in Pediatrics with ACTH and Cortisone. J. N. Etteldorf. —p. 273.
Effects of Cortisone and Adrenocorticotropic Hormone (ACTH) in Arthritis. F. E. Tatum.—p. 278.
Collagen Diseases and Allergy. C. J. Deere.—p. 282.
ACTH and Cortisone in Miscellaneous Medical Conditions. H. S. Tacket.—p. 285.
Cortisone and ACTH in Surgery. R. H. Patterson.—p. 289.
Primary Tuberculosis of Adenoids in 28-Year-Old Nurse: Case Report. J. T. Bryan.—p. 293.

Wisconsin Medical Journal, Madison

50:633-732 (July) 1951

Pain Relief in Labor and Choice of Anesthesia. R. E. McDonald and W. K. Hoffman.—p. 655.
Spina Bifida and Its Associated Malformations. D. M. Pick.—p. 659.
Disturbances of Behavior in Children Following Asphyxia Neonatorum. M. E. Sattler.—p. 664.
*Carcinoma of Rectum and Sigmoid. A. G. Martin.—p. 667.
Torsion of Appendix of Testis: Review of Literature and Presentation of Case. R. I. Bender.—p. 670.
Low Spinal for Delivery Using Procaine or Pontocaine. E. A. Steffen and D. L. Ashton.—p. 673.

Carcinoma of Rectum and Sigmoid.—This report is based on observations on 44 consecutive patients, all personally examined and operated on by Martin in the past eight years. Colostomy was done in three of the patients, palliative resection in five, and resection with the expectation of cure in 36 patients. The author concludes that if every effort is made to resect the zones of spread as well as the primary cancer, a large number of patients will be saved. Not all of them may remain well for five years, but all are made more comfortable. Periodic follow-up examinations are important, because in these patients cancers are prone to develop in other parts of the large intestine and possibly also in other organs. Of the 27 patients of this group operated on five or more years ago, 13 are living and well, eight died of recurrence, five died of other causes, and one died after operation.

FOREIGN

Archiv für Gynäkologie, Munich

179:495-614 (No. 5) 1951. **Partial Index**

Resorption and Elimination of Sulfonamides in Puerperium. E. J. Welling and F. J. Diensberg.—p. 514.
Cause of Infantile Mortality During Last Months of Pregnancy, Delivery and Postpartum Period. L. Seitz.—p. 545.
Influence of Desoxycorticosterone Acetate on Chloride and Urea Content of Serum. H. Haberland.—p. 578.
*Changes in Width of Pupils During Rhythm of Menstrual Cycle. G. K. Döring and E. Schaefers.—p. 585.

Changes in Width of Pupil During Menstrual Cycle.—In six healthy women ranging in age from 19 to 34 years, the width of the pupil was measured daily during 23 menstrual cycles. At the same time ovarian function was studied by measuring the basal temperature. It was found that the pupil was contracted more during the premenstrual than during the postmenstrual period. This is caused by the predominance of the parasympathetic tonus shortly before menstruation and for the first day or two of the period. A pupillary contraction of brief duration was also noted between periods. Since it precedes the temperature jump by two days, this intermenstrual pupillary contraction can be taken as a sign of the rupture of the follicle. These changes in the pupil apparently are related to the fluctuations in the tonus of the sympathetic that occur in the menstrual cycle. It is also suggested that there might be a connection between the tonus of the sympathetic nervous system and the fluctuations in the sex hormone content of the blood.

Archives Françaises de Pédiatrie, Paris

8:461-572 (No. 5) 1951. **Partial Index**

Chronic Anemia with Arrest of Normoblastic Maturation. (Blackfan-Diamond Type). M. Lelong, R. Joseph, C. Polonowski and others.—p. 473.
Hypoplastic Anemias of Infants, with Reference to the Communication by Lelong and Joseph. J. Bernard, S. Isreman and M. Hovasse.—p. 486.
*Immunization with Pertussis Prophylactic Vaccine. R. Debré and J. Zourbas.—p. 490.
*Treatment of Pertussis with Hyperimmune Human Serum: Report of 555 Cases. R. Debré, F. Herzog and J. C. Guérin.—p. 501.

Immunization with Prophylactic Pertussis Vaccine.—During a period of 30 months starting October, 1947, three injections of Hemophilus pertussis vaccine containing a total of 50 billion organisms were given to 300 infants and children between the ages of 2 months and 5 years. The interval between the injections was one month for the children aged less than 2 years, and 15 days for the children between 2 and 5 years. An American and later a French vaccine, both in concentrations of 20 billion pertussis organisms per cubic centimeter adsorbed on aluminum hydroxide, were used. The French vaccine was partly "detoxified" with formaldehyde. In more than one-third of the children who received the American vaccine, local reactions occurred at the site of the injection within 8 to 10 days. These consisted of subcutaneous nodules, which persisted for three to five weeks. A sterile abscess occurred in one instance. Neither nodules nor abscesses were observed in the children to whom the French vaccine was administered. Systemic reactions to both the American and French vaccines were rare and consisted of a rise of temperature to 100.4 F. In three infants a temperature of 104 F. occurred for 24 hours. There were no neurological signs, but administration of the vaccine was discontinued. Four children between the ages of 20 months and 3 years who received the French vaccine had a nocturnal paroxysmal cough after each injection or for 24 hours two to four days after the first injection. Thirty months after the first injection, all the children tested had antibody titers of 1:320 or more, an indirect proof of adequate immunity. In only 4 of 44 immunized children who were exposed to infection with H. pertussis did the disease develop and then only in a benign form. The remaining 40 had become immune.

Hyperimmune Human Serum in Pertussis.—An effective human pertussis hyperimmune serum was prepared from the pooled blood of 200 donors, each of whom had been given a total of 110 billion Hemophilus pertussis organisms in four injections of ½ to 2 cc. of 20 billion organisms per cubic centimeter at weekly intervals. This serum was used prophylactically in 60 children and young adults who had been exposed to pertussis, and therapeutically in 495 children with pertussis. Of the 60 exposed persons, no pertussis developed in 49, 8 had mild pertussis, and 3 had moderately severe pertussis. Of the 495 children with pertussis, 39 were given the hyperimmune serum in the catarrhal stage of the disease, and 456 in the paroxysmal stage. Of the 39, no paroxyms developed in 6, 21 had mild whooping cough, 10 had moderately severe whooping cough, and only 2 had severe paroxysms. Excellent results were obtained in 136 of the 456 children in the paroxysmal stage, good results in 153, and fair results in 53. Treatment failed in 107, and 7 died. Those patients in the paroxysmal stage of the disease to whom the hyperimmune serum was administered early, i. e., during the first 10 to 14 days of the disease, obtained the best results. The smallest dose administered was 60 cc., but this dose can be increased in patients whose agglutinin titer has been less than 1:320. The serum was not very effective in the treatment of mild cases of pertussis. In severe cases and in infants the first injection should be given in two to four divided doses to prevent severe undesirable effects. The serum did not seem to have any favorable effect on pulmonary or cerebral complications of pertussis. As a rule, the serum was well tolerated. One case of hepatitis was reported five months after an injection of hyperimmune serum, but no definite relationship between the icterus and the administration of the serum could be demonstrated.

British Heart Journal, London

13:273-420 (July) 1951

*The Liver in Heart Failure: Relation of Anatomical, Functional, and Circulatory Changes. S. Sherlock.—p. 273.
Effect of Priscol on Peripheral Venous Pressure. K. Braun and C. H. Fryd.—p. 294.
Circulation Time as Clinical Test. H. Kopelman.—p. 301.
Electrocardiographic Changes in Chronic Cor Pulmonale. J. A. Kilpatrick.—p. 309.
Cardiac Infarction with Pain Confined to Effort. E. G. Wade and A. M. Jones.—p. 319.
Clinical Significance of Gallop Rhythm in Hypertension. B. E. Miles.—p. 327.
Peripheral Circulatory Changes Associated with Arteriovenous Aneurysms. G. M. Wilson.—p. 334.
The Heart in Myotonia Atrophica. J. D. Spillane.—p. 343.
Further Experience with Khellin in Angina of Effort. H. A. Dewar and T. A. Grimson.—p. 348.
Hypertonic Salt Solution Intravenously as Test for Coronary Disease. T. Bardin and T. Doliopoulos.—p. 353.
Calcification of Aortic Valve and of Coronary Arteries. D. Pyke and C. Symons.—p. 355.
*Dissecting Aneurysm of Aorta in Mother and Child. G. J. Griffiths, A. P. Hayhurst and R. Whitehead.—p. 364.
Variability of Ventricular Potentials at Diaphragmatic Level of Oesophagus. I. G. Kroop, M. F. Steinberg and A. Grishman.—p. 369.
Lung Volume in Low Output Cardiac Syndromes. D. G. B. Richards, A. G. W. Whitfield, W. M. Arnott and J. A. H. Waterhouse.—p. 381.
Endocardial Fibrosis. I. R. Gray.—p. 387.
Complication Following Coronary Sinus and Cardiac Vein Catheterization in Man. J. McMichael and J. P. D. Mounsey.—p. 397.

The Liver in Heart Failure.—A congested "nutmeg" liver is a common postmortem finding in patients dying from heart failure, and the studies reported here were concerned with the correlation between functional changes and hepatic histology in heart failure. Sections of liver were obtained by aspiration biopsy or by necropsy from 50 patients in congestive heart failure. Changes occurring in the agonal and immediate postmortem periods were such that necropsy sections proved unreliable for assessing the effects of cardiac failure on the liver. Biopsy specimens showed that centrilobular hepatic necrosis occurred almost invariably. If the heart failure worsened, the necrosis spread peripherally, whereas if the cardiac condition responded to treatment, the liver lesion healed. Connective tissue changes originated at the center of the liver lobules. Reticulin condensation occurred first; this was followed by reticulin proliferation and eventually by spread of connective tissue from a central vein to adjoining central veins, producing cardiac cirrhosis, which became latent if the heart disease was amenable to treatment. Structural changes in the liver seemed related to circulatory changes, namely, to reduction in cardiac output, diminution of the arterial oxygen saturation, height of the hepatic venous pressure, and also to the duration of heart failure. A raised serum bilirubin level was common;

jaundice was rare and was usually found only in patients with mitral stenosis and tricuspid valvular incompetence. The mean serum bilirubin value was higher in the patients with the severer grades of hepatic cell necrosis. Patients with deep jaundice tended to have very high auricular pressures. The power to excrete sulfobromophthalein fell with increasing severity of liver cell necrosis. Urine urobilinogen was increased. Bilirubin was often detected in the urine. It is concluded that cardiac cirrhosis has no specific clinical, blood biochemical, or circulatory associations, and that it does not cause intrahepatic portal venous obstruction. Cardiac jaundice is a complex disorder, in that support can be found for hepatocellular, obstructive, and hemolytic theories. In most patients multiple factors are present.

Dissecting Aneurysm in Mother and Son.—A woman, 34, complained that she easily became tired and exhausted. She had borne four children. The fourth child was one month premature and lived for only two weeks; the cause of death is not known. The mother died on the ninth day after this confinement. The anatomic diagnosis was ruptured dissecting aneurysm of the abdominal aorta and atheroma of the aorta. The woman's first child, a boy, who died suddenly at 14 years of age, had found physical exertion exhausting, but otherwise had been normal. Only part of the aneurysm from the boy was available for study. No lesion that might have initiated the dissection was found. There was mucoid change in the inner media, but the dissection lay in the outer media. The association between dissecting aneurysm and pregnancy in the mother may be due to the softening of connective tissues that occurs in pregnancy, and further work is needed to determine whether the aorta is among the organs affected. Mucoid change in the aorta may be simply one among many manifestations of a type of change occurring in intercellular tissues in general. Clinically, dissecting aneurysm is likely to be mistaken for coronary disease or an acute abdominal emergency, its most characteristic feature being a sudden attack of severe pain in the chest or abdomen. The relationship of the two patients suggests the possibility of a hereditary predisposition and the need of investigating the family history in this disease.

British Journal of Surgery, Bristol

38:401-542 (April) 1951

Biopsy of Rectum. W. B. Gabriel, C. E. Dukes and H. J. R. Bussey.—p. 401.
Chronic Empyema. T. H. Sellors and G. Cruickshank.—p. 411.
Ligation of Aorta and Use of Cellophane for Abdominal Aneurysm. H. J. Croot.—p. 432.
*Some Observations on Diagnosis of Clinically Pigmented Skin Tumours. M. R. Ewing and T. Powell.—p. 442.
Anatomy of Oblique Proximal Septum of Pulp Space. J. L. Wilkinson.—p. 454.
Ectopic Ureter in Childhood: With Account of Four Personal Cases. A. J. Alldred and T. T. Higgins.—p. 460.
Small-Gut Obstructions Following Combined Excision of Rectum: With Special Reference to Strangulation Round Colostomy. J. C. Goligher, O. V. Lloyd-Davies and C. T. Robertson.—p. 467.
Malignant Disease of Testis: With Special Reference to Radiotherapy. T. M. Prossor.—p. 473.
*Acute Renal Failure: Two Cases Treated by Decapsulation and Peritoneal Dialysis. D. W. Bracey.—p. 482.
Looser-Milkman Syndrome: Occurrence in Case of Idiopathic Steatorrhoea. C. Strang.—p. 489.
Portal Embolism Following Thrombosis of Splenic Vein, and Causing Infarct-Like Cyanotic Atrophy ("Zahn's Infarcts") of Liver: Complication of Splenectomy Performed in Course of Total Gastrectomy. W. St. C. Symmers.—p. 498.
Appendiceal Calculi: Report of Two Cases and Brief Review of Literature. C. F. Chapple.—p. 503.
Regional Colitis as Acute Abdominal Emergency: Report of Three Cases. T. J. Brownlee.—p. 507.
Carcinoma of Epididymis. R. Whitehead and A. F. Williams.—p. 513.
Mediastinal Neuroblastoma in an Infant. R. C. Alexander.—p. 517.

Pigmented Skin Tumors.—The occurrence of sclerosing angioma, a not uncommon pigmented skin tumor, is reported in 11 patients, six women between the ages of 19 and 56 and five men between the ages of 17 and 71. In two of the patients the tumor simulated very closely in its history and its appearance a malignant melanoma, with which it is often confused. In one of these two patients extensive resection was carried out, leaving the young woman with a disfiguring scar and troublesome recurrent edema of the foot and ankle. There is no certain way clinically of distinguishing between the pigmented sclerosing angioma that is clinically benign and the malignant melanoma. Diagnosis can be made only by the most careful microscopic examination establishing the nature of the hemosiderin pigment by iron stains. In the surgical management of any pigmented skin tumor that cannot be diagnosed with certainty by clinical methods alone, the first step should be in every case a wide local excision, to be followed later by a dissection of the regional glands only when a diagnosis of malignancy has been confirmed. Review of sections of 123 clinically pigmented skin tumors revealed a high proportion of erroneous diagnoses. A significantly large number of the tumors, both benign and malignant, were epithelial in origin. On microscopic examination the sclerosing angiomas were observed to compose a surprisingly high percentage (8%) of the entire group, while a clinical diagnosis of sclerosing angioma was not made in a single instance.

Acute Renal Failure.—Two patients, a girl 14 and a man 48, with acute renal failure were treated successfully by bilateral decapsulation of the kidneys. Renal failure was precipitated by 18 gm. of sulfamerazine administered for tonsillitis in one patient, and by several hundred 5 gm. tablets of acetylsalicylic acid (aspirin), swallowed in an attempt to commit suicide, in the other. The intense congestion of each kidney was evident at operation, and the manner in which immediate expansion took place after stripping strongly suggested that the kidneys were under great tension. During the first 24 hours after operation the peritoneal cavity of the first patient was irrigated three times with 2,000 cc. of isotonic sodium chloride solution, each irrigation being spread over approximately seven hours; in the second case peritoneal lavage was performed with 34 liters of isotonic sodium chloride solution instilled in 17 intermittent injections of two liters each, 15 liters being obtained by siphonage. In the first case 2.8 gm. of urea was removed via the peritoneal cavity, and in the second case 42.9 gm. was removed. It was felt that the peritoneal dialysis played only a small part, if any, in the patients' recovery. When peritoneal dialysis is employed, isotonic sodium chloride solution should also be used, but this solution should be run in rapidly and as rapidly removed, with no interval between cessation of instillation and the start of evacuation. It is suggested that decapsulation of the kidney allows the cortex to expand, thus relieving the anoxia consequent to circumferential pressure and associated vasospasm. The decision to decapsulate depends on the response to paralysis of the sympathetic nerve. If there is no return of function within a few hours of such paralysis then the operation should be undertaken without delay. Failure to relieve suppression by decapsulation will occur when cortical necrosis is already far advanced, where stripping is prevented by previous disease, and when there is persistent and unsuspected fetal lobulation of the kidneys.

Hospital, Rio de Janeiro

40:1-146 (July) 1951. **Partial Index**

*Streptomycin in Whooping Cough. R. Montenegro.—p. 51.

Dihydrostreptomycin in Whooping Cough.—Montenegro administered dihydrostreptomycin sulfate to 134 infants and children between the ages of 6 months and 5 years with whooping cough. The drug was given in one daily dose of 0.5 or 1 gm. for seven consecutive days. Sulfadiazine was also given, for the first four days of treatment, in four fractional doses up to a daily dose of 0.5 or 1 gm. In all cases cough diminished in frequency and in violence within the first three days of treatment. Cure, during the week in which the treatment was given, was obtained in 80 patients (60%). In the remaining 54 patients (40%) the disease took a mild course during the first week and was controlled one week after discontinuation of the treatment. There were neither complications nor deaths. The patients gained weight. During 18 months of follow-up, they were in normal health.

Journal of Laryngology and Otology, London

65:461-548 (July) 1951

Review of Tuberculosis of Upper Air Passages During Past 30 Years and Its Treatment by Streptomycin. F. C. Ormerod.—p. 461.
Toxic Effect of Streptomycin on the VIII Cranial Nerve. J. A. B. Thomas.—p. 472.
Electro-Encephalography in Relation to Otorhinolaryngology. J. D. Spillane.—p. 477.
Difference Limen of Intensity Variations of Pure Tones and Its Diagnostic Significance. E. Lüscher.—p. 486.

BOOK REVIEWS

The Kidney: Medical and Surgical Diseases. By Arthur C. Allen, M.D., Pathologist, James Ewing Hospital, New York. Cloth. $15. Pp. 583, with 1115 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1951.

Increased interest in renal disease has been aroused in recent years by important contributions to our knowledge of renal pathology and physiology. Although there are several current books dealing with various phases of the subject, this book is a welcome addition. The author refers to his book as an atlas and textbook of renal diseases with emphasis on dynamic rather than on static descriptive pathology. Since the pathologist of today is necessarily interested in both the physiological and the clinical manifestations of diseased tissue, the author's clinical evaluations of the various pathological lesions make this book of particular value. In interpreting histological abnormality, the author uses all available clinical and physiological data and integrates them with the pertinent physiological disorders they reflect. Although the book is replete with interesting discussion of the various phases of renal pathology, those sections devoted to the various types of nephrosis are outstanding and most instructive. Of particular interest is the discussion of renal pathology found with hemoglobinuric nephrosis, which often is referred to as lower nephron nephrosis. The section devoted to diseases involving the blood vessels is also outstanding.

Renal pathology usually is divided into two distinct sections, one devoted to diseases claimed by internal medicine, and the other to renal infection and so-called surgical diseases. Although this artificial division still is maintained in the practice of medicine, this book emphasizes the close interrelation of all types of renal disease and the necessity of having a comprehensive knowledge of all phases of renal pathology in attempting intelligent clinical interpretation. It should be of great value to every clinician and particularly to the modern urologist, who finds that a knowledge of pathology involving electrolytic and fluid balance is imperative. It is possible that urologists might regard some of the chapters devoted to so-called surgical disease of the kidney as inadequate. The book is exceptionally well illustrated. The numerous photomicrographs are excellent and show the various histological changes with outstanding clarity. Taken as a whole, the book offers to anyone interested in renal disease an excellent opportunity to become acquainted with modern concepts of renal pathology.

A Text-Book of X-Ray Diagnosis, by British Authors, in Four Volumes. Volume I. Edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., Director, X-Ray Diagnostic Department, University College Hospital, London, and Peter Kerley, M.D., F.R.C.P., F.F.R., Director, X-Ray Department, Westminster Hospital, London. Second edition. Cloth. $12. Pp. 434, with 439 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C.2, 1951.

Formerly published in three volumes, in 1939, this work has been rewritten and expanded into four volumes, so divided that they may be utilized separately by readers interested in radiology of limited areas or systems. This volume, titled "Head and Neck," embraces the central nervous system, including the spinal cord, the teeth and jaws, the eyes, the accessory nasal sinuses, and the temporal bone. Like the companion volumes, it is outstanding in its completeness, is interestingly written, beautifully and adequately illustrated, and detailed in its coverage of anatomy, physiology, pathology, radiographic technique, and interpretation of radiological findings.

The section on the central nervous system occupies more than half the volume. In addition to radiography of the cranium, ventriculography, encephalography, and cerebral angiography are thoroughly discussed and illustrated. The chapter on the spinal cord is well illustrated, and discussion of technique and interpretation of myelography is adequate.

Detailed discussion and illustration of normal teeth and jaws open the second section, which occupies 60 pages. Typical examples of anomalies and diseases of the teeth, periodontal membrane, and alveolus follow. The section concludes with a discussion of the temporomandibular joint. In this section, the radiographic illustrations are of the "negative" type, in which radio-opaque tissues appear white, whereas in the remainder of the volume, radiographic illustrations are reversed or "positive" radio-opacity appearing dark. The American reader is accustomed to, and usually prefers, the negative type of illustrations but quickly becomes adapted to the reverse, particularly when the illustrations are excellent, as in this volume.

The section on the eye emphasizes the localization of foreign bodies in and around the eye. Parts four and five, on the accessory nasal sinuses and the temporal bone, should be of interest to the otorhinologist as well as the radiologist. The necessity for close cooperation between the clinician and the radiologist is pointed out, and the radiologist is urged to acquire a thorough knowledge of the clinical aspects of disease in this area. In fact, teamwork between the clinician and radiologist might be said to be the keynote of the entire work. All physicians working in the fields covered will enjoy and learn from this volume, as well as from others in the set.

Introduction to Motherhood. By Grantly Dick Read, M.A., M.D. Cloth. $1.75. Pp. 104, with 22 illustrations. Harper & Brothers, 49 E. 33rd St., New York 16, 1950.

This small book has been written primarily for the woman who is having her first baby. In the initial chapters the discussion of the physiology of reproduction is much too sketchy for even the lay person. The theory and practice of natural childbirth are presented, and the advantages are cited. The emotional factors in pregnancy, labor, and delivery are portrayed realistically. A chapter is devoted to the husband and wife relationship, in which the family unit is emphasized. The role of the husband and father is stressed.

In spite of many virtues, this book is not suitable for American women. The author's harangue about operative obstetrics, analgesia and anesthesia, and the untrustworthy physician will certainly decrease the patient's confidence in her medical attendant and create the very fear that engenders tension and pain. "Is modern intelligent woman still willing to be tampered with and humiliated? Surely she is not too nervous to demand what she wants and believes to be right. Is there no sense of shame in the ignominy of lying, powerless and paralyzed, while her baby is extracted by instrumentation?" Such statements do not inspire confidence in the patient's physician and destroy much of the value of lay education.

This book is not recommended for obstetric patients, since it is felt that it will do more harm than good for the cause of natural childbirth.

Microbiology for Nurses. By Mary Elizabeth Morse, M.D., Martin Frobisher, Jr., S.B., Sc.D., Chief, Bacteriology Section, United States Public Health Service, Communicable Disease Center, Atlanta, Ga., and Lucille Sommermeyer, R.N., B.S., M.Ed., Nurse in Charge, Nursing Research Laboratory, United States Public Health Service, Communicable Disease Center, Atlanta. Eighth edition. Cloth. $4. Pp. 540, with 208 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C.2, 1951.

This is a good and readable handbook of bacteriology, written by three authors with long experience in education and writing. Several excellent illustrations, well-chosen and extensive bibliographies, and numerous, reliable tabulations were added in this new edition. The classification follows that of Bergey's "Manual of Determinative Bacteriology" and, unfortunately, does not always list synonyms under which the respective micro-organisms frequently appear in the medical literature. Thus the teacher using this otherwise excellent manual will have to supplement it with a dictionary.

The reviews here published have been prepared by competent authorities and do not represent the opinions of any official bodies unless specifically stated.

Therapy of Dermatologic Disorders Including a Guide to Diagnosis and a Dermatologic Pharmacopeia. By Samuel M. Peck, B.S., M.D., Dermatologist to Mount Sinai Hospital, New York City, and George Klein, M.D., Associate Visiting Dermatologist, Morrisania City Hospital, New York City. Cloth. $6.50. Pp. 383, with 4 illustrations. Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, 1951.

The authors state that their primary intention in writing this volume was to compile a dermatologic pharmacopeia. As they wrote the work, they became convinced of the desirability of including the indications for the use of the drugs and prescriptions listed. The descriptions of various skin diseases in the book are on the whole brief and elementary, and intended only as a "good guide for the beginner in dermatologic therapy." The pharmacopeia portion, which comprises one-third of the volume, is for the guidance of experienced dermatologists.

While there is much useful information in the book, which is to be expected in view of the outstanding reputation of the senior author in particular, it is doubtful that much clarification is given many aspects of dermatologic therapy, because of the numerous alternate methods of treatment, new and old, that are listed. This apparent attempt at completeness will be a source of confusion to the beginner in dermatologic therapy in selecting the method of treatment to be used in a particular patient.

There is little question that general practitioners and specialists in fields other than dermatology have difficulty in classifying many conditions affecting the skin and in selecting methods of treatment that, at least, are not likely to do harm. External therapy for skin diseases may be divided into three general types: (1) methods that, if employed for the proper condition accurately diagnosed, rapidly produce cure or improvement in almost all cases, e. g., benzyl benzoate therapy for scabies, (2) methods that have little specific effect but have the virtue of not interfering with the return of the skin to normal, e. g., potassium permanganate foot soaks in acute fungous infections, and (3) methods in which the potentiality for harm exceeds the potentiality for good, e. g., sulfonamide ointments.

Part 1 of this volume is devoted to a guide to diagnosis. This consists principally of line drawings of the face and of the anterior and posterior surfaces of the trunk and extremities, on which many superimposed key numbers refer to short descriptions of 52 dermatologic conditions listed in the following pages. While topographic diagnosis is a useful device, one might have difficulty in using the drawings and corresponding differential diagnostic lists, so that actually they have little value. The lack of photographs in any book dealing with dermatologic diagnosis is a serious drawback.

Part 2, the major portion of the volume, includes a classification of skin diseases, with suggestions for appropriate treatment. The system of classification, always difficult in those dermatologic diseases for which the principal etiological agent has not been determined, is good. Some sections, for example, that on chemical contact dermatitis, are well done. The clinical descriptions are in general brief, and rare conditions frequently receive as much space as conditions that are much commoner. This portion of the book seems to have been written hurriedly, with little regard for consistency of style or editorial construction. Even a moderately sensitive reader is jarred by phrases such as "a positive transient Wassermann. . . ." When is a Wassermann "transient"? Reference to the well-known American physician J. F. Schamberg as "I. F. Schamber" and to Paul's test for herpes simplex as "Poul's" test are examples of numerous proof errors.

Much present-day dermatologic disability results from reactions to topical treatment. Certain methods deserve mention in a book of this type only to warn against their use. It is surprising, therefore, that Peck and Klein recommend sulfonamide and penicillin ointments for a variety of superficial bacterial infections, since their continued use induces sensitivity in a high percentage of patients. Other examples of methods that are unsafe or dubiously effective include the use of boric acid compresses in the treatment of acute infantile eczema and the use of stibophen (fuadin®) in creeping eruption and in granuloma venereum. As an alternate method of treatment of scabies, sulfur should be used in a strength of not over 10%, not 10 to 30% in petrolatum. Carbon dioxide snow in the treatment of nevi and other lesions of the skin is mentioned without warning. Pigmented nevi should never be treated in this way. The limitations and contraindications of surgical diathermy are not clearly outlined.

Probably the commonest form of dermatitis is that due to poison ivy. Certain methods of treatment recommended by the authors might well be questioned, including topical application to opened blisters 10% to 15% tannic acid solution in 80% alcohol, which is painful on raw surfaces, and, in extensive dermatitis, involves danger of liver damage from absorption of tannic acid. The rationale of painting the areas with 2% ferric chloride solution, or of giving vitamin C orally, is questionable. Spraying of the individual lesions with ethyl chloride "until the skin shows the first signs of freezing" is hardly a method to be used by an inexperienced physician, if by anyone.

Part 3, the dermatologic pharmacopeia, contains much useful information and much that is obsolete; it could well have been reduced one-half. The "uses" must be accepted with caution in some instances; they may not be in accord with directions elsewhere in the book. For instance, injections of rhus extract are outlined for the treatment of poison ivy dermatitis on page 328, though the authors do not favor this method on page 120. These injections often do harm, and never do good, during the acute phase of the dermatitis. Acid nitrate of mercury is mentioned as a "topical agent for destroying epithelioma." "Destroying" is a strong term in this connection; such methods have no place in the treatment of skin cancer.

This volume is not so useful as it could have been. The excellent portions are marred by material that is obsolete or carries considerable risk to the patient. The manuscript would have benefited from liberal use of a blue pencil and more painstaking editing and proofreading.

Lehrbuch der Chirurgie. Herausgegeben von Prof. E. Gohrbandt, Prof. E. v. Redwitz, und Prof. F. Sauerbruch. Bearbeitet von Prof. W. Anschütz, et al. Begründet von Prof. L. Wullstein und Prof. M. Wilms. Band I: Allgemeiner Teil. Chirurgie des Kopfes, des Halses, der Brust, des Bauches, der Harn- und Geschlechtsorgane. Band II: Chirurgie der Wirbelsäule, des Beckens, der Extremitäten und des vegetativen Nervensystems. Tenth edition. Cloth. 58 marks; 40 marks. Pp. 940, with 661 illustrations; 660, with 560 illustrations. Gustav Fischer, Villengang 2, Jena 15b, Germany, 1951.

The first edition of this work was published in 1908 under the title "Textbook of Surgery." In 1909 a second volume appeared, edited by Wullstein and Wilms. After the death of Wilms, Kutner became co-editor. Wullstein died in October, 1930. Twenty-two authors contributed to this edition. The tremendous progress made in surgery during the past 20 years, particularly in surgery of the thorax and the vegetative nervous system, has culminated in this new two-volume edition.

Volume 1 deals with the general principles of surgery, including that of the head, neck, chest, abdomen, genitals, and reproductive apparatus. A detailed review of such a work would take one too far afield; in general, it may be stated that this is one of the best textbooks on surgery to appear in the German language. The various chapters are written by contributors recognized in the surgical literature as authorities. A great deal of information is made available to those who read German.

It may be pointed out, however, that, although the presentation is exemplary from the etiologic, pathologic, and diagnostic points of view, the descriptions of various operative technics are overcondensed. The work can be highly recommended as a textbook or teaching aid on the general principles of surgery, but not as a guide to operative procedures.

The second volume deals with surgery of the spine, the pelvis, the extremities, and the vegetative nervous system.

As is generally realized, during the recent wars the European countries suffered from severe shortage of materials, and the advances made, particularly in anesthesia and surgery of the thorax, could not possibly keep pace with those made in the United States. The progress made despite these serious handicaps is remarkable.

The second volume provides an illustration of the overcondensation already referred to. The section on surgical diseases of the biliary passages begins with an introduction explaining the physiopathologic background, which is excellent. Inflammatory processes of the biliary passages are also well discussed. Under a subheading here the authors describe very ably the

type of inflammation that may involve the gallbladder and the extrahepatic biliary passages without gallstones. This is followed by a full discussion of cholelithiasis. The chapter is highly instructive as to etiology, differential diagnosis, and many other points, but the operative procedures are too briefly sketched. Cholecystectomy is dismissed in one brief paragraph; so is choledochotomy. Only two short paragraphs are allotted to the important subject of repair of injured gall ducts.

In the section on surgery of the pancreas the arrangement is similar to that of the preceding chapter, but not a single illustration accompanies the text on the technics used in various modern surgical procedures. For carcinoma of the pancreas the authors merely advise the creation of an anastomosis between the gallbladder and the stomach. No mention is made of the detailed work done in this country and elsewhere on malignant pancreatic disease. The same applies to surgery of the spleen.

In the chapter on surgery of the stomach and duodenum, one finds an excellent review of modern concepts of disease of these organs; here again the presentation of technics is abbreviated and lacks detail. The material on surgery of the bowel, as well as that on several other important subjects, must call for the same objection.

Nevertheless, the work as a whole should be welcomed by those who read German. It contains a great deal of mature experience and observation, and it is up-to-date. The paper and the illustrations, some of which are in color, are very good.

The Postnatal Development of the Human Cerebral Cortex. Volume IV: The Cortex of the Six-Month Infant. By J. LeRoy Conel, Research Associate in Pathology, Children's Medical Center, Boston. Cloth. $12.50. Pp. 191; 108 plates. Harvard University Press, Cambridge 38, Mass., 1951.

The first three volumes of this work were devoted to the cortex of the newborn, the one-month-old infant, and the three-month-old infant and were published in 1939, 1941, and 1947, respectively. In the present volume, the first section is devoted to a description of the microscopic appearance of various areas of the cortex. This includes cyto-architecture, the fiber pattern, and the myelination. This is a very detailed, Germanic study. It is probably more precise than the material warrants. Measuring the thickness of the cortex and its various layers in millimeters to the third decimal place is ridiculous and results in apparent differences which are neither reliable nor significant. Also, designating the various parts of the precentral gyrus in accordance with the part of the body which is presumably represented there is neither precise nor accurate. Representation is too diffuse and inconstant from individual to individual, and the ideas as to localization vary too widely with different investigators. It would have been far more satisfactory had the author provided a map showing the point from which the sections in question were taken.

The descriptive section of 157 pages is followed by a section of 20 pages which discusses this material and compares it with the brains previously examined and described, particularly those of three-month-old infants. The principal differences are that the cortex has become wider, and, as the cells have not increased in number, they are more widely spaced. The degree of change varies in different areas. The sizes of the nerve cell bodies show little change. The amount of chromophil substance in the cytoplasm increases with age, and it appears to originate from the nucleus. The intracellular neurofibrils are also more advanced in their differentiation in the older brains, and the dendrites and axones increase in size, length, and compactness. The number of terminal bulbs on the ends of dendrites which lie on the cell membranes is increased. The number and size of fibers originating outside of the area of cortex studied and the number of myelinated fibers are increased. Throughout the brain, myelination is much more advanced in the six-month-old brain. On the basis of all criteria used, area FAγ, or the precentral area gigantopyramidalis, is more advanced in development than any other area in the six-month-old brain.

The third section of the book is composed of tables giving various average measurements from different parts of the cortex.

The last section consists of 108 plates, each containing two figures. The first 98 plates illustrate various areas of the cortex as stained by three different methods—cresyl violet for nerve cell bodies, Cajal's method for nerve fibers and neurofibrils, and Golgi-Cox for the total cell, along with drawings. The next three plates are Golgi-Cox preparations of sections from various afferent centers, showing the heavy band of fibers in the fourth layer in these areas. The last seven plates are Pal-Weigert preparations to show the degree of myelination in various areas. In the main, these are excellent figures and well reproduced. On the whole, those prepared by Cajal's method are the least satisfactory. Figures 74, 90, 153, 169, and 173 are particularly poor.

This book has been prepared with loving care and has been done well, as have its predecessors. It is the only thoroughly detailed source of information on the subject.

Atlas der Elektrokardiographie: Eine Einführung in die moderne elektrische Herzuntersuchung für den praktischen Arzt und den Studenten. Von O. Ritter und V. Fattorusso. Cloth. 35 Swiss francs. Pp. 256, with 219 illustrations. S. Karger, Holbeinstrasse 22, Basel; 215 Fourth Ave., New York 3, 1951.

One is at first tremendously impressed with this atlas, but closer examination reveals some flaws. It becomes evident that this is a report of the experiences obtained by the authors while working with Frank N. Wilson in Ann Arbor, Mich., and R. F. Ziegler in Detroit, and of their reading of the works of H. Schaefer in Germany, P. W. Duchosal in Switzerland, L. Deglaude and J. Lenègre in France, M. Segers in Belgium, E. Sodi-Pollares in Mexico, as well as a digest of the monographs of Ashman and Hull, Bayley, Bernstein, Cabrera, Craib, Goldberger, Holzmann, Katz, Lepeschkin, Lewis, Mann, Myers, Pardee, Scherf and Boyd, Stratton, Rothberger and Winterberg, and Wenckeback and Winterberg. As a consequence, this booklet contains the viewpoints of several authorities paraphrased by the present authors without being thoroughly integrated. There are many contradictions. Some sections are inadequate, particularly the section on heart strain and heart hypertrophy. The outstanding feature of this book is its diagrams, some of which are very illuminating and educational. They are for the most part original or reprinted illustrations with modifications. Their examination and study will more than repay the reader for the effort involved.

This booklet will be of value to the experienced electrocardiographer who can read German, and especially to the European cardiologist, in orienting him as to modern trends, because the authors ably present the recent developments in the field. It is hoped that in the next edition the authors will attempt to present a more unified point of view.

Introductory Chemistry for Students of Home Economics and Applied Biological Sciences. By Lillian Hoagland Meyer. Cloth. $5. Pp. 532, with illustrations. The Macmillan Company, 60 5th Ave., New York 11, 1951.

This appears to be an excellent elementary textbook in general chemistry, including biological chemistry. However, its scope, examples, and illustrations are so strongly slanted toward women specializing in foods, nutrition, or textiles—women who probably will have no other course in chemistry—that one wonders why students of applied biological sciences are mentioned in the subtitle. Surely student nurses could be taught better from one of the existing textbooks slanted toward nursing. The following serious error appears on page 121: "The rate at which a radioactive element disintegrates depends on the concentration of the element present. . . ."

Introductory College Chemistry. By Harry N. Holmes. Fifth edition. Cloth. $4.75. Pp. 594, with 180 illustrations. The Macmillan Company, 60 5th Ave., New York 11, 1951.

This standard textbook has been revised extensively since 1946. It now covers atomic energy and fission, incorporates recent views on atomic structure and relationships of the elements and stresses current technology, e. g., of titanium and antibiotics. This modernization is accomplished without loss of the important "classical" matter. The book should serve not only college freshmen, to whom it is addressed, but also those who wish to bring up-to-date their knowledge of inorganic and general chemistry. Illustrations, printing, and binding are excellent.

QUERIES AND MINOR NOTES

TREATMENT OF CATARACT

TO THE EDITOR:—*Please discuss medical treatment of very early cataract. Has succus Cineraria maritima been proved of any value in postponing or preventing the usual surgical treatment?*

M.D., Pennsylvania.

ANSWER.—There is no scientific evidence to indicate that any eye drop, subconjunctival injection, local remedy, or indeed any type of ocular therapy is of any value in slowing the progression of a cataract or in reversing the changes already present. Except in the rare types of cataract due to hypoparathyroidism or to the ingestion of certain poisons, there is no general treatment of any avail. Treatment of the hypoparathyroidism or withdrawal of the causative poison may prevent further deterioration in these uncommon cataracts but will have no effect on the opacities already present.

Almost every adult has lens opacities which do not interfere with vision and which cannot be seen except with the slit lamp microscope and with the pupil dilated. With aging there is gradual sclerosis of the lens nucleus together with coalescence of pre-existing opacities and the formation of additional opacities, so that the changes of cataract are almost universal in persons past 70. Obviously, only a minute percentage of these cataracts ever progress to a point where the visual defect so interferes with the patient's vocation or avocation that surgery is indicated. The factors that cause a cataract to progress relatively rapidly in one person and slowly in another are entirely unknown.

A large number of remedies have been proposed for the treatment of cataract. To a large extent the reputation that temporarily attaches to such therapy is due to the slow progression of many cataracts independent of any treatment and to the visual betterment that occurs spontaneously owing to refractive changes in the lens; the delay and improvement are readily attributable to the nostrum.

Accurate diagnosis of the nature and the position of the cataract, with exclusion of other disease of the eye, is the first step in treatment. Glaucoma, which occurs commonly in the same age group, must be excluded, so that a progressive loss of vision will not be mistakenly attributed to cataract instead of glaucoma, for which there is effective therapy. Correction of nutritional and metabolic disturbances and deficiencies is indicated on general principles, but there is no valid evidence that this is of any value except in hypoparathyroidism.

Useful vision may be maintained for long periods with conscientious and frequent correction of the changing refractive error. Unless there is a secondary condition other than cataract necessitating removal, extraction of the lens is not indicated until there is serious interference with the patient's way of life. Since the two eyes will not work together after the lens of one is removed, there is no optical indication for removal of a monocular cataract when corrected vision in the better eye is more than 20/70.

SULFONAMIDES AND DRAINS IN PERITONEAL CAVITY

TO THE EDITOR:—*In the light of present surgical knowledge are the uses of such things as sulfonamides and drains in the peritoneal cavity no longer acceptable? If so, when did they become unacceptable?*

M.D., North Carolina.

ANSWER.—One of the committees of the National Research Council studied the local application of sulfonamides and presented a report before the meeting of the American Surgical Association in 1943. This was published in the *Annals of Surgery* **118**:171 [August] 1943). The studies of this committee revealed that concentration of the sulfonamides was best obtained by parenteral administration. With the advent of the antibiotics, which are so effective in the prevention and control of infections, there has been a drastic reduction in the indications for the use of the sulfonamides if the antibiotics are available for use.

The matter of drainage of the peritoneal cavity still remains a problem of individualization, with regard both to each particular case and to the experience of each surgeon. Some authorities, even with the use of the antibiotics, have continued to insert a drain in the peritoneal cavity in most cases of localized abscess and whenever fistulous discharge was anticipated.

NEGATIVE BLOOD WASSERMANN REACTION WITH POSITIVE SPINAL FLUID

TO THE EDITOR:—*Please advise me how often the cerebral spinal fluid is found to be positive for syphilis when the blood serum is negative.*

R. R. Ivey, M.D., Morganton, N. C.

ANSWER.—According to Stokes and associates (Modern Clinical Syphilology, Ed. 3, Philadelphia, W. B. Saunders Company, 1944, p. 992) Menninger and Bromberg (1935) found among 500 cases of various types of neurosyphilis with positive spinal fluids that 31% had negative blood serologic reactions. In an extended study Blalock and Hinsie (1938) noted that 8.1% of all patients with general paresis, irrespective of the kind of treatment they received, had a negative blood Wassermann reaction prior to therapy. This corresponds with the observation by Kierland, O'Leary, and Vandoren (1942) that 8.8% of paretics, untreated with arsenicals, had positive spinal fluid serologic reactions and negative blood serologic reactions and that 10.4% of paretics treated with arsenicals prior to the tests showed the same discrepancy.

More recently Thomas (Syphilis: Its Course and Management, New York, The Macmillan Company, 1949, p. 52), reported that only 3% of "tabetics with evidence of syphilitic activity, as demonstrated by spinal fluid findings at Bellevue Hospital, had completely negative blood tests for syphilis."

TUBERCULIN TESTING

TO THE EDITOR:—*For routine use in office practice, what strength purified protein derivative and old tuberculin would you recommend for skin testing? After purified protein derivative or old tuberculin is diluted, how long can one rely on the potency of the solution for skin testing? Is the patch test with these products dependable?*

F. A. Stewart, M.D., Colorado Springs, Colo.

ANSWER.—Purified protein derivative (PPD) is what the name implies, "purified," and is therefore more specific in its action than old tuberculin (OT). There are many nonspecific proteins in the bouillon residue of old tuberculin which in stronger dilutions may elicit reactions resembling true tuberculin reactions. In weaker dilutions, however, there are no interfering factors, so that any postitive results in low dilutions may be accepted as true tuberculin reactions. The only positive advantage of old tuberculin over purified protein derivative is that of cost. When large surveys are made, old tuberculin is much less costly. Nothing stronger than first-strength purified protein derivative or 1:10,000 dilution of old tuberculin (0.01 mg.) should be used in any unknown case. Stronger dilution will cause painful reactions and sometimes sloughing in strongly positive cases. The weaker dilutions will find most active cases of tuberculosis. If suitable diluents or buffer solutions are used, the preparations may be used for several weeks if kept on ice. It is advisable, however, to make them up fresh each time if possible.

The patch test is least dependable of all but may be useful in children and thin-skinned white young adults. In most other persons the reaction is many times obscured or actually is not elic-

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any official bodies unless specifically stated in the reply. Anonymous communications and queries on postal cards cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

ited, owing to the texture and color of the skin. The old tuberculin is specific in the lower dilutions, but purified protein derivative is specific and accurate under all conditions and can be recommended as the most efficient and most suitable for all purposes.

USE OF NOSE DROPS IN CHILDREN

TO THE EDITOR:—*In our outpatient clinic we have been debating whether the use of mild vasoconstricting nose drops (phenylephrine [neo-synephrine®] hydrochloride 0.25%) in children under 6 years of age with coryza and secondary infection is of value in reducing the incidence of acute otitis media. The difference of opinion of several young doctors from different medical schools is amazing. Your opinion would be appreciated.* *M.D., California.*

ANSWER.—Mild, slightly acid, isotonic nasal vasoconstrictors are among the more useful drugs that can be employed in the nasal cavity of infants and young children. The weight of evidence indicates that these drugs afford symptomatic relief only and are not curative. Nasal vasoconstrictors can relieve nasal congestion for varying periods of time, promote comfort, improve nasal ventilation, and, when judiciously employed, promote adequate drainage from paranasal sinuses by opening obstructed ostia. Even temporary relief from nasal obstruction is a boon to the child so afflicted, and a number of sympathomimetic amines have come to assume a legitimate place in treatment.

Because acute rhinitis in infancy often produces complications, it demands adequate attention. When the infant cannot take the breast or bottle because of breathing difficulty due to suppurative nasal blockage, use of a soft rubber syringe to clear the nasal passages and the application of a mild nasal vasoconstrictor are most helpful. In children, nasal infection strikes at virgin territory, absorption is more rapid, and therefore the constitutional symptoms are frequently more pronounced than in adults. Sinus ostia in children are relatively large and permit access of infected secretion from the nasal passages. Many persistent or recurring colds are due to infection of the maxillary sinuses and the ethmoid cells.

Most cases of acute suppurative otitis media follow the introduction of micro-organisms into the middle ear cavity by way of the eustachian tube as a result of an acute inflammatory process in the nasopharynx. While actual proof may be lacking, by improving nasal ventilation and establishing drainage from the paranasal sinuses, nasal vasoconstrictors constitute a potential, and sometimes actual, contributing factor to the reduction of acute otitis media.

DRY AIR IN THE HOME

TO THE EDITOR:—*Is information available on the optimum humidity percentages that are recommended for residential dwellings, with particular reference to the influence on upper respiratory tract infections? Will you kindly refer me to source material in this regard?*

Howard L. Penning, M.D., Springfield, Ill.

ANSWER.—There is no factual information on the optimum humidity in homes from the standpoint of upper respiratory infections. Although the drying of the mucous membranes of the nose and throat may produce a somewhat unpleasant sensation in a few persons who are sensitive to low humidities, most of the difficulties attributed to dry air are fictitious.

REFERENCES:

1. Winslow, C. E. A.; Herrington, L. P., and Nelbach, J. H.: Influence of Atmospheric Temperature and Humidity upon Dryness of Oral Mucosa, Am. J. Hyg. **35**: 27 (Jan.) 1942.
2. McCord, C. P.: Diseases of Respiratory Tract and Air Conditioning, J. A. M. A. **116**: 1360 (March 29) 1941.
3. McConnell, W. J.: Investigations of the Health Aspects of Air Conditioning, Refrig. Eng. **31**: 79 (Feb.) 1936.
4. Bristol, L. D.: Air-Conditioning and Industrial Health, J. A. M. A. **110**: 2142 (June 25) 1938.
5. Dunklin, E. W., and Puck, T. T.: Lethal Effect of Relative Humidity on Air-Borne Bacteria, J. Exper. Med. **87**: 87 (Feb.) 1948.
6. Howell, W. H.: Humidity and Comfort, Science **73**: 453 (April 24) 1931.

USE OF UNSTERILIZED HYPODERMIC NEEDLES

TO THE EDITOR:—*Many cases of human serum jaundice may have resulted from the use of hypodermic needles that were put back into test tubes and plugged in with cotton but not resterilized before subsequent use on another patient. What methods of avoiding such re-use of needles have been developed? Is there any way to seal sterilized needles unmistakably in the operating room with materials that the operating room nurse can quickly and efficiently handle?*

M.D., Kansas.

ANSWER.—The fact that such cases occur reflects not only human fallacy but inadequate or insufficiently rigid control of aseptic procedures. The problem posed is one that is recognized as a potential hazard in the transmission of infection. It has been suggested that the needles be placed within folds or envelopes of foil or other heat-resistant materials prior to enclosure in a test tube and the foil discarded when the needle is used. Utilization of a new envelope would be required prior to subsequent sterilization. Sterilization indicators also could be adopted, provided they were discarded when the tube was opened. Regardless of the labeling procedure employed, strict enforcement by close supervision of the program adopted is imperative. It is always safe, when in doubt, to resterilize.

GYNECOMASTIA IN A YOUNG BOY

TO THE EDITOR:—*A 14-year old white boy has gynecomastia. He has a normal deep male voice, a soft beard, a moderate amount of axillary and pubic hair, and fair development of the penis and testes. The main difficulty is psychic, when exposed in the showers at school. What is the accepted treatment?* *John D. McCausland, M.D., Chula Vista, Calif.*

ANSWER.—Gynecomastia may be produced in various ways. It is commonly associated with hypogonadism, and sometimes the correction of hypogonadism either with chorionic gonadotropin or androgenic therapy will reduce the size of the breasts. The patient should be examined carefully. If hypogonadism is present, appropriate therapy should be given. In rare instances gynecomastia is associated with a tumor of the testis which produces estrogen. If all forms of therapy fail to correct the gynecomastia, the breast tissue may be removed surgically.

DISPOSABLE TRANSFUSION SETS

TO THE EDITOR:—*Please send information regarding percentage of pyrogen and chemical reactions in blood transfusions from the use of the disposable transfusion sets with plastic tubing as compared to that of the ordinary transfusion sets with rubber tubing. Which of the two sets is considered more satisfactory?* *M.D., New York.*

ANSWER.—The director of one institution that purchases about 10,000 disposable transfusion sets per year reports that he knows of no pyrogenic or chemical reactions being attributed to the use of these sets. Disposable sets may be more expensive than ordinary sets. However, most—if not all—of them are produced by manufacturers with considerable experience in preparation of blood transfusion equipment, and they are subject to controls not ordinarily employed by smaller laboratories.

HYPOSPADIAS

TO THE EDITOR:—*What is the best time to operate on hypospadias in the male? One of my patients is 1 year old; another is 6 years old. Both children have a dimple at the side of the urethral opening. About 0.5 cm. below this dimple, there is a pinpoint opening, from which the urine comes.*

Ludwig Gruenewald, M.D., Sheboygan, Wis.

ANSWER.—The time to operate on a patient with hypospadias is debatable. Some urologists believe in early operation, but the majority believe in waiting until the organ has developed somewhat in size. As a rule, if the urethral orfiice is just behind the normal opening in the region of the sulcus, it is best not to operate. When the opening is at the penoscrotal junction, the condition requires a series of operations. Six years of age is considered a good time to start.

URINARY INFECTION AMONG TRUCK DRIVERS

To the Editor:—*Among military truck drivers in a combat zone, there is a disproportionately large number of acute and chronic urinary infections among those who must drive usually 10 to 15 hours daily over exceedingly rough roads. Has any connection been established between heavy driving activities and kidney infection? If so, are wide, supporting "kidney belts" of any prophylactic benefit?*

M.D., California.

Answer.—Inquiry among various urologists who have treated truck drivers in both military and nonmilitary areas fails to corroborate the increased incidence of urinary infection among truck drivers. Lowered resistance, resulting from fatigue and rigorous weather conditions, might permit such infection. The increased incidence of urinary infection in trench warfare is an example of this. Continued and heavy drinking is another factor that would lower resistance against infection. It is doubtful that jerking of the kidneys by rough driving would in itself cause infection. It is also doubtful that renal supports ("kidney belts") would be of any prophylactic benefit.

CYSTITIS FOLLOWING NEPHRECTOMY

To the Editor:—*Please discuss the causes of persistent severe cystitis following a nephrectomy for tuberculosis. In my patient, the other kidney apparently is normal.*

A. Pirrone, M.D., Cleveland.

Answer.—If cystoscopic examination has not disclosed a stone or a tumor, then one is justified from the history in assuming that the patient has tuberculosis of the bladder, secondary to the tuberculosis of the kidney that was removed. It is not uncommon for the bladder symptoms to persist after the kidney has been removed. The length of time that it takes for the bladder symptoms to disappear will be about the same as the duration of the bladder symptoms before the nephrectomy. In other words, if the patient had bladder symptoms for two years before the kidney was removed, it will take two years for them to disappear. Local treatment seems to have little influence on the symptoms, and many urologists refrain from local treatment. The internal administration of sandalwood oil or methylene blue may relieve the bladder symptoms.

SNEEZING IN SUNLIGHT

To the Editor:—*Many persons sneeze on stepping into sunlight. By what pathways is the sneeze produced?*

M.D., California.

Answer.—This seems to be a simple reflex and not an allergic phenomenon. But such reflex sneezing seems to be unexplained. It is not adequately described in any of the standard texts on ophthalmology or neurology. The matter has been discussed with experts in neuroanatomy, physiology, ophthalmology, otolaryngology, and neurology, and from none of them was it possible to obtain a satisfactory explanation.

The sneezing may not be the result of exposure to light but may rather be the result of a cold blast of air striking the cornea or nasal mucous membrane. This would involve a reflex passing over the ophthalmic or nasal branch of the trigeminal nerve back to the brain stem and in some way activating the respiratory center and the vagus nerve. A combination of stimulation of the retina by light entering the eye and stimulation of the cornea by a blast of air might be a precipitating cause.

MALARIA PROPHYLAXIS

To the Editor:—*Please tell me what is the most acceptable drug for use in prophylaxis for malaria in traveling through southern Asia, particularly India?*

Harold W. Morgan, M.D., Mason City, Iowa.

Answer.—The two most acceptable suppressive drugs for malaria are chloroquine (aralen®) or camoquin® (4-[7-chloro-4-quinolylamino]-alpha-diethylamino-ortho-cresol. These products have been used extensively in investigative programs, and the former has been used by the armed forces with outstanding success in Korea, where malaria is very prevalent. With the dosage recommended there are no undesirable reactions and administration is simple. The dosage for chloroquine is two tablets once weekly, each tablet containing 0.25 gm. of chloroquine phosphate. The dosage for camoquin® is also two tablets per week. These tablets are made in only one size.

These suppressive drugs will only prevent the disease as long as they are being taken. After returning from an endemic area all travelers should bear in mind the possibility of malaria if fever develops and should place themselves in the hands of a physician promptly.

OPHTHALMIC OINTMENT BASE

To the Editor:—*On page 691 in Queries and Minor Notes in* The Journal, *June 16, 1951, is a paragraph regarding ophthalmic ointment base. The implication of the answer to a question from Dr. Walter Weinberger is that penicillin would be appropriately used in an ointment base using aquaphor® or a base containing 25% wool fat. It has been our experience that wool fat is not a suitable ingredient for penicillin ointments and that rapid deterioration occurs when wool fat is one of the components. I do not know whether the deterioration is due to one of the normal constituents of wool fat or to trace elements of metals, such as copper, picked up by the refining equipment. I do know that there is rapid deterioration, so that the ointment is far substandard in strength within a month.*

I am acquainted with aquaphor® but have never made any experiments to determine the stability of penicillin ointments in that base. Obviously, if the ointment base containing 25% wool fat recommended in The Journal *were to be used in a prescription and the entire amount used very soon, no trouble would be expected; however, if any of the ointment were unused, it should be discarded. We know too, however, that patients are prone to leave unused medicaments around, thinking that they might come in handy sometime. In such a case it could happen that, if the ointment were not kept under refrigeration, some portion might be used after it had lost its efficacy. The patient might then improperly criticize the physician for prescribing something that was not serviceable, and both physician and patient might be led astray as to the efficacy of the type of treatment. In my opinion, the best base for a penicillin ophthalmic ointment is petrolatum thinned to a suitable texture that will vary with the type of petrolatum but will contain around 20 to 25% of liquid petrolatum.*

I have read The Journal *for nearly four decades. I know that it has a world-wide influence. I hate to see recommended in your pages something that I know from painful experience not to be advisable.*

C. O. Ewing, Chief Chemist,
Rexall Drug Company, St. Louis.

To the Editor:—*Lanolin (wool fat) should not be used in the preparation of penicillin ointment, owing to the fact that certain lots of lanolin rapidly inactivate penicillin. Thus, the use of lanolin in compounding this prescription is hazardous. Actually, many of the manufacturers making penicillin ointment utilize lanolin, but each batch has to be carefully checked to be sure that it will not cause deterioration of the drug. To my knowledge no one has yet found why certain batches of lanolin cause destruction of penicillin. It appears, however, that the inactivation of penicillin by lanolin is due to extraneous material and not to a normal constituent of lanolin.*

If penicillin ointments are made with water soluble bases the penicillin (crystalline sodium or potassium) in such preparations will lose potency relatively rapidly. Procaine penicillin, being relatively insoluble, maintains its potency in water bases. Petrolatum is satisfactory in an ointment base but, of course, does not produce the best pharmaceutical preparation.

Henry Welch, M.D.
Director, Division of Antibiotics
Food and Drug Administration
Washington 25, D. C.